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MEDICINAL CHEMISTRY

IN TWO VOLUMES

Volume I

MEDICINAL CHEMISTRY

Chemistry, Biochemistry, Therapeutic and Pharmacological Action of Natural and Synthetic Drugs

ALFRED BURGER
ASSOCIATE PROFESSOR OF CHEMISTRY
UNIVERSITY OF VIRGINIA

VOLUME I

1951

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ERRATA: Medicinal Chemistry, Volume I

Page 177, formula (XI-56): add CH_3 to N.

Page 202, formula for Novaspirin: add CO_2H in ortho position of benzene ring at left.

Page 238: change "VERATRINE" to "VERATRUM" in first heading.

Page 239, line 11, compound should read: 2-methyl-5,9,9-dimethoxyfuranochromone.

Page 290, Figure 1, lower left: change "Sacial" to "Sacral."

Page 298, last line: change "aminopropanol" to "aminopropane."

Page 307, Section a: change "Nethacol" to "Nethamine."

Page 310, second line of equations: insert "$CH(CH_3)$" in both compounds.
left-hand formula, third line of equations, should read:

$$C_6H_5CH_2CH(NHCOCH_3)CH_3.$$

line 2 of text below equations, compound should read: N-acetylamphetamine.

Page 398, formula (XXII-15): omit the two subscripts 3 following the parentheses.

Page 399, line 6 above footnotes, compound should read:
2,5-bis-methylamino-p-benzoquinone.

Page 426, line 2 above formula (XXIII-56): change "choline benzilate" to "benzilyloxyethyldimethylethylammonium chloride."
formula (XXIII-56), change to:

$$(C_6H_5)_2C(OH)CO_2(CH_2)_2N^+(C_2H_5)(CH_3)_2 \cdot Cl^-$$

Page 443, line 3: Change "his" to "her."
line 7: Change "He" to "She."

Page 449, Section e: Omit "Thenfadil."

Page 451: Omit "Thenfadil."

Page 452, Omit "Hydrillin" from first column.

Page 466, line 12: Change "late" to "lenate."

PREFACE

Interest in medicinal chemistry has been high during the last two decades all over the world, and particularly in the United States. It has been stimulated by improved methods of clinical diagnosis and the ensuing demands for new corrective and curative agents, by the need for better medicinals in the treatment of the growing number of aged individuals, by the urgency of wartime search for anti-infectious drugs, by the greater stature of pharmacological theories, and by the unprecedented expansion of the American pharmaceutical industry. The elucidation of the structure of most vitamins, and of many endocrine products, and the beginning of an appreciation of their biochemical mechanism of action have contributed to the rapid development of this field. There is barely a meeting of learned societies in the chemical, biological or medical sciences at which some thoughts and facts about drugs are not discussed in countless papers and symposia, and the increasing number of participants in these meetings has taxed the capacity of even large auditoriums. More and more young scientists are turning to the manufacturing, testing and theoretical study of medicinals as a productive and intellectually rewarding occupation.

It appears timely to present a treatise on medicinal chemistry as a survey of various phases of the field, and as a contribution to its future development. Individual monographs dealing with specific classes of drugs have been published in adequate numbers and afford the opportunity of complete bibliographies of the respective fields. Several recent excellent books on fundamental theories of chemotherapy have unified our ideas of drug action. Good texts explaining the most important facts about useful drugs to students of pharmacy are also available. This treatise is addressed principally to the more advanced reader, and hopes to familiarize him with past achievements of medicinal chemistry, with current thoughts and hypotheses, and with the direction of needed research in the whole field.

It is obvious that one individual cannot hope to possess a complete and detailed knowledge of a vast and diversified borderline field. The presentation of all details by a cooperative effort of specialists would fill twenty volumes instead of the two allotted to this book. The author will be grateful to his readers for pointing out any errors in fact or interpretation, and for suggesting improvements of the text for future use. Several sections of the book have been read by other chemists. Dr. William L.

Truett has read the introductory chapters; Dr. Richard O. Roblin has critically read Chapter XXXII; and Dr. James W. Cole has made helpful suggestions and additions to Chapter XLI. The author is grateful for their assistance, and also for Dr. Hans R. Rosenberg's review of Chapter XXVIII. The latter has also facilitated the composition of this chapter by granting permission for the broad use of his monograph, *The Vitamins*, and his chapter in *The Chemistry and Technology of Food and Food Products*. The whole text has been read by Mr. David F. Hinkley. Dr. Leo Stevens of Philadelphia has called the author's attention to many important references in the biological literature. The Publisher's staff has aided tirelessly with helpful suggestions and advice.

In the course of preparing the manuscript, a number of books were consulted frequently and the author wishes to take this opportunity to express his indebtedness to the following sources: Fränkel, *Die Arzneimittelsynthese*, sixth edition, 1927; Slotta, *Grundriss der Modernen Arzneistoff-Synthese*, 1931; I. G. Farbenindustrie, *Medicine in Its Chemical Aspects*, 1933; Fischl and Schlossberger, *Handbuch der Chemotherapie*, 1935; Small, Mosettig, Eddy and Himmelsbach, *Studies on Drug Addiction*, 1938; Rosenberg, *Chemistry and Physiology of the Vitamins*, 1945; Wiselogle (editor), *Survey of Antimalarial Drugs*, 1947; Bovet and Bovet-Nitti, *Médicaments du Système Nerveux Végétatif*, 1948; Northey, *The Sulfonamides and Allied Compounds*, 1948; Fieser and Fieser, *Natural Compounds Related to Phenanthrene*, third edition, 1949; Henry, *The Plant Alkaloids*, fourth edition, 1949; and Work and Work, *The Basis of Chemotherapy*, 1949.

A short index serving as a guide to the most important data presented in the first twenty-eight chapters appears at the end of Volume I. A comprehensive index for both volumes will be found at the conclusion of Volume II.

This book has been written in the author's spare time, after a full load of teaching and research, between the Fall of 1947 and Spring of 1951. The writer's wife, Frances Page Burger, deserves thanks for not minding too much twelve hundred quiet evenings while the manuscript was being prepared.

Charlottesville, Virginia
April, 1951

ALFRED BURGER

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CHAPTER I

Introduction

Medicinal chemistry is an applied science whose fundamental roots lie in all branches of chemistry and biology. The term "pharmaceutical chemistry" is often substituted for "medicinal chemistry," particularly in its industrial ramifications where the compounding of drugs to materials useful in pharmacy commands considerable attention.

The purpose of medicinal chemistry is the elucidation of the structure and the synthesis of compounds which can be used in medicine for the cure or the treatment of disease. Moreover, it is concerned with the understanding of the chemical and biological mechanisms by which the action of drugs can be explained. Medicinal chemistry also tries to establish relations between chemical structure and biological activity, and to link the latter to the physical properties of the drugs.

The true medicinal chemist regards the sciences that contribute to his own as tools, but he must be well versed in them in order to achieve his goal. Because he works in an applied borderline field, he must know many phases of the sciences which funnel information into his own. A medicinal chemist must be experienced in organic chemistry, physical chemistry, and biochemistry, pharmacology, microbiology, and many phases of medicine pertinent to his work. Even though he may be expert in only one or two of these sciences, his acquaintance with the others will enable him to bridge gaps of knowledge and to paint a composite picture of a situation the specialist in one field could barely achieve.

On the other hand, half-measures are not enough to attain scientific results, and even a close acquaintance with a field is insufficient to work out details. Therefore, the medicinal chemist is necessarily a member of a research team which usually consists of him, a pharmacologist who tests his drugs, physicians who transpose animal experiments into clinical trials, and a chemical engineer who manufactures the tested and proved drug for general therapeutic use. The great results of recent medicinal researches have all been obtained by research teams, and not by individual scientists.

In return for the aid the contributing sciences render medicinal chemistry, the latter has given chemical, biological, and engineering sciences a new impetus in fields which had been dormant because of lack of interest

in a given field. The discovery of the medicinal usefulness of an obscure compound has always stimulated inquiry into the reactions and improved methods of preparation of similar substances, and almost in every instance has led to purely theoretical developments no longer connected with medicinal applications. Likewise, methods of pharmacology and biology have had to be improved and revised to meet the peculiarities of new drugs, and the experiments performed in these studies have inevitably clarified underlying biological mechanisms. Finally, the manufacture of an unusual drug necessitates new designs in equipment and new methods which inevitably solve the problems of other industrial procedures.

One of the prime motives of medicinal chemistry is service to medicine. Some of the proudest and most spectacular achievements of medicine have been made possible by chemists and chemical engineers who, in turn, have shared in the satisfaction of the service they have rendered.

Many medicinal chemists are so engrossed in preparing, analyzing, testing, and applying drugs that they overlook one fundamental aspect of their science—and of all science. Medicinal chemistry may have been stimulated by the need of the sick for drugs, or even by the commercial rewards of their manufacture. But what the science of medicinal chemistry has achieved is the product of the ideas of thousands of persons whose driving motive has been scientific curiosity, and an urge to explore relations between fundamental sciences. The great advances of the past have come from the keen interpretation of often accidental and unforeseen observations, and research organizers should keep this in mind for attaining future decisive results.

I. THE SCOPE OF THIS BOOK

This book makes an attempt to present to the reader the wide and ramified field of medicinal chemistry as it has been pictured above. It hopes to go beyond the scope of many other compendia on drugs which have been concerned with the structural analysis and the synthesis of important medicinal chemicals. These subjects will be treated carefully but not to the exclusion of other aspects of drugs. On the whole, the derivation of the structure of a naturally occurring drug will be discussed only if the particular case has not been reviewed in a readily accessible book or journal. Important modes of synthesis will be given for representative drugs, and the reactions involved should be understood readily by any chemist with some graduate training.

The methods of biological testing will be reviewed briefly for each class of drugs. In every chapter, the therapeutic usefulness as well as the medical or veterinary drawbacks will be pointed out, but a sincere effort has been made not to encroach upon the realm of the physician. It is

often difficult to draw a line between chemical pharmacology and medicinal chemistry, and only differences in emphasis and point of view separate these fields. Throughout this book emphasis has been placed on chemical aspects, and it is not anticipated that a physician will be able to construct a prescription from the facts stated in the text. However, this book will acquaint him with the background and with newer developments of drugs and give him an appreciation of the scientific work in other fields that has made his therapeutic tools possible.

The greatest progress in medicinal chemistry has come from the application of modern biochemistry to its problems. This happy coordination has furnished an explanation of the mechanism of action of a number of drugs and has raised medicinal chemistry from an empirical art to a science. Every attempt has been made in this book to point out the advantages of this approach, and it is the author's hope that the stature of medicinal chemistry among fundamental sciences will be heightened by this mode of presentation.

Even though the biochemical approach has proved so valuable for the development of our subject, it has actually raised more questions than it has answered. As fascinating as this situation is in promoting further research, it has led to a state in which overcautiousness and excessive speculation without experimental facts have alternated constantly. This volume is trying to avoid both these extremes. There can be no advance without imagination, and speculation about biochemical mechanisms of drug action has been admitted where it appears to further the subject constructively. The expert biochemist may feel that the rigid lines of scientific conservativism have been broken in some instances. On the other hand, drawbacks of methods and compounds have been pointed out consistently at all occasions as a caution against overestimating their effectiveness.

The text has been documented extensively but not exhaustively. Since this book is intended as a textbook on a professional level, and not as a reference book, no attempt has been made to furnish a complete bibliography. No author should feel offended if a particular paper of his has not been quoted. The scope of the book is so wide that a selection of subjects has been imperative. Additional information on details omitted here may be obtained from pertinent monographs and review articles.

There is no space in one book for a complete account of the thousands of compounds that have been tested biologically and found inactive. Knowledge of such "negative experiments" is important if it teaches us that an approach which might have been expected to be successful has been eliminated from consideration by experimental findings. But the random inclusion of chemicals that have been screened for every kind of physio-

logical activity because they were handy in a given laboratory cannot be expected within the framework of a graduate-level textbook. Emphasis has therefore been placed on positive results, with proper reference to exceptions to "rules" and other experiments which permit a critical evaluation of the therapeutic achievements of medicinal chemistry.

1. Structure and Enzyme Inhibition

A number of statements appeared in the biochemical literature prior to 1940 which suggested that the true cause of the interference of a drug with the normal course of an enzymatic reaction should be sought in a structural overlapping of drug and normal substrate (metabolite). These thoughts were given a firm foundation by the work of Woods and Fildes, who demonstrated the first clear-cut example of such close structural relations for the pair sulfanilamide-*p*-aminobenzoic acid. This discovery has produced the metabolite-antagonist theory, one of the most fruitful ideas in organizing contradictory and apparently random observations about relations of chemical structure and biological action. Because of the importance of this working hypothesis, a separate chapter (XXXII) has been devoted to it.

2. Arrangement of Drugs on the Basis of their Medicinal Use

The uncertainties of the relations of chemical structure and biological activity make it appear unwise to arrange all drugs from a purely structural point of view. Alcohols are known to exert hypnotic, analgetic, and antibiotic properties. Amines are found in the series of analgetics, vasopressors, antihistaminics, bacteriostatics, and antimalarials. Phenolic groups are present in antiseptics, autonomic drugs, trypanocidal agents, estrogenic hormones, and certain vitamins. Lactones are encountered among cardiotonic and anthelmintic drugs. This enumeration could be extended to almost every other kind of structural unit and biological action. Since even the concept of drugs as inhibitors of enzyme systems still lacks experimental support in a few series of compounds, a general survey of medicinal chemistry will arrange drugs most advantageously according to their practical use. The Table of Contents takes this arrangement into account. Drugs acting on various functions of the body (functional or pharmacodynamic drugs) are followed by drugs used in combatting pathogenic parasites (antiseptics, chemotherapeutics, etc.). A few special chapters (antimitotics, hormones, vitamins) are interspersed at appropriate places.

II. THE NAMING OF ORGANIC MEDICINALS

The most adequate means of naming organic drugs is to follow the systems generally accepted for the nomenclature of all organic compounds. The scientific reports on the chemistry of a drug, its degradation, analysis, synthesis, reactions and physical properties almost always attempt to give the material the most rational name at least once.

By the time the substance reaches the pharmacologist or biologist who is interested in some of its physiological properties, it is often advisable to identify it by a brief number or name. It has become customary in many laboratories to code compounds for biological testing with consecutive numbers, the initials of the chemist, or the research team that prepared or first tested the drug. The pharmacological literature is full of these code designations, and it is not always easy to trace the chemical identity of the coded substance.

If the drug has been prepared in an industrial laboratory, and has shown promise in pharmacological tests, it will usually be distributed in experimental quantities to physicians for trials in man. In order to facilitate the naming of the drug by the medical profession, especially if the chemical name is long and cumbersome, a more easily pronounceable name is printed on the label. Whether or not this remains the name under which the drug will be marketed depends on a number of circumstances.

It used to be the custom to let the name point out the application of the drug. Such names as Analgen, Anesthesin, Streptocide, Antimalarin, Hypnon, Urotropin, Antifebrin, and hundreds of others are examples of this procedure. This practice has been condemned by medical and pharmaceutical societies in the United States because it was feared that the names might imply to the layman that the particular brand of the drug was *the* medicinal agent for a certain condition, and that desirable commercial competition between manufacturers would thus be impeded. In other countries which do not regulate monopolistic tendencies as it is done in the United States, this way of naming drugs is still widely practiced.

The naming of drugs produced by the pharmaceutical industry has given the linguistic imagination of the advertising departments free rein. Euphonious combinations of letters without any hint as to the nature of the medicinal are invented by psychologists who feel that the commercial success of the material may be enhanced in this way. More often, however, a simplified contraction of the chemical name is arranged in a tasteful manner. It would be hazardous to draw any conclusions from such names, but they constitute perhaps the most desirable mode of pharmaceutical

nomenclature. The name of the manufacturer has occasionally been woven into the name; alliterations of related drugs are quite common. Dozens of local anesthetics end in *ocaine*, borrowed from cocaine. Many barbiturates have the ending *al* in common, probably because they were intended to improve upon Veronal, and analogs of ephedrine often end in *edrine*, etc.

Considerable confusion is introduced into nomenclature when the so-called generic name of a drug begins to appear in the literature. After a manufacturer has given a drug his trade-marked name, he usually submits an alternate name to the Council of the American Medical Association. If the Council accepts this name and places it in the periodical publication, *New and Non-official Remedies* (NNR), any other manufacturer who has the right to market the product can use this officially approved name. The generic name together with the dosage and other vital information must appear on the label of the container of the drug. These regulations are subject to Federal Laws known as the "Pure Food and Drug Act".

Two examples may illustrate this procedure. 1-Phenyl-2-aminopropane has been used as a pressor agent and central nervous stimulant under the brand name of Benzedrine. Its generic NNR name, accepted at a later date, is amphetamine, and is used by other manufacturers who do not own the registered trade name.

In a similar manner, the hormone of the adrenal medulla was isolated, identified, and synthesized early in the century and named Adrenaline. Many years later, the generic name epinephrine was accepted by the Council, and the drug is now described under either designation.

A formal argument about the mode of spelling the brand name versus the officially accepted name of NNR or the *Pharmacopoiea*, the final authority on drug standards, has been settled through the agreement that brand names should be capitalized. This does not contribute much to prevent confusion that arises when the often less well-known NNR names supplant well-established brand names. Also, drugs originating in foreign countries have often become known and established by their original names before another name is given them in this country. The antimalarial Plasmochin was known for about fifteen years under this label before the NNR name pamaquine began to supersede it. Widely known drugs such as Aspirin are often not capitalized although this name was originally a manufacturer's trade mark for acetylsalicylic acid.

In this volume, all brand names will be capitalized in the index; moreover, the new designation of trade names by the American Medical Association[1] will be used, in which the name is followed by the symbol®. Thus, the names will read as shown in Table I.

[1] "The Rules of the Council on Pharmacy and Chemistry," *J. Am. Med. Assoc.*, **140**, 678 (1949).

TABLE I. EXAMPLES OF TRADE NAMES AND GENERIC NAMES

Trade name	Generic name
Adrenalin®	Epinephrine
Benzedrine®	Amphetamine
Chloromycetin®	Chloramphenicol
Dolophin®	Methadon

The difficulties of identifying a popular drug in the medical literature of the world are emphasized by a glance at the trade names of sulfanilamide.[2] No less than sixty names have been used for this one compound. An international authority correlating the efforts of the pharmacopoieas of the many nations of the world would be welcomed by all members of the chemical and medical professions.

Many commercial names are designations for salts of physiologically active bases with common acids, or of physiologically active acids with common bases. Novocaine, e.g., is a brand name for procaine hydrochloride. Since the common acids or bases in these salts are merely adjuncts to the medicinal and confer upon it desirable properties such as crystallizability, stability, and solubility, the brand names of the salts are often more widely used than the official names of the active component. In this volume, no serious effort has been made to separate such overlapping usages. Names like Novocaine and procaine have been used interchangeably with the full understanding that the reader will direct his attention solely toward the pharmacologically important component of the drug. The use of the trade name of a salt for the trade name of a base or acid could cause occasional discrepancies in quantitative evaluations of drug activity, and every effort has been made to express clearly in such instances which of the materials has been the subject of the respective measurements.

Throughout the text, cross-references to footnotes to other chapters will be designated by chapter number and footnote number (see example on page 8, XXXV[7]). Cross-references to formulas are designated by chapter number and formula number (see example on page 9, XL-6).

[2] Northey, *The Sulfonamides and Related Compounds*. Reinhold, New York, 1948, p. 636.

CHAPTER II

Historical Development of Medicinal Chemistry

The history of a science is composed of the ideas and facts which have advanced the borders of contemporary knowledge. It is an account of feats of imagination and careful correlation, high-lighted by those rare sparks of scientific insight which draw novel conclusions from a few significant observations. The great advances of medicinal chemistry have been achieved by two types of investigators: those with the genius of prophetic logic who have opened a new field by interpreting correctly a few well-planned experiments; and those who have varied patiently the chemical structures of physiologically active but toxic compounds until a useful drug could be evolved as a service to medicine.

More than in any other branch of science, empirism has been employed in medicinal chemical research, and the formulation of basically sound ideas has taken place hesitantly only during the last fifty or sixty years. This may appear as a long period in comparison with still younger sciences, such as biochemistry, nuclear physics, etc., but the bulk of defendable theories of medicinal chemistry has actually been developed only during the past twenty-five years.

This comparatively short period of serious scientific growth of our field opens the question as to when the history of medicinal chemistry has really started. It may seem purely philosophical to ask what constitutes a medicinal chemist. We do not subscribe to the notion that, long ago, Chinese emperors or Roman philosophers were medicinal chemists. Yet, some of these historic figures are usually credited with having been the forerunners of modern pharmacy and pharmaceutical science since their empirical methods of collection and therapeutic administration of herbs and herbal concoctions evoke an echo in the present-day selection and medical study of botanical drug mixtures.

The oldest records of therapeutic plants and minerals stem from the ancient civilizations of the Chinese, the Hindus, the South American Mayas and the Mediterranean peoples of antiquity. The scholar-Emperor Shen Nung (2735 B.C.) compiled a book of herbs and is credited with observing the antifebrile effects of Ch'ang Shang which has been shown recently to contain antimalarial alkaloids (XXXV[7]). He also noticed the

diaphoretic and stimulatory effect of the drug Ma Huang from which, almost 5000 years later, Chen isolated the active alkaloid ephedrine (XIX-23).

Other oriental civilizations have also left us records of their uses of medicinal plants. The antileprotic action of the chaulmoogra fruit was known to the ancient Indians, and the ipecacuanha root was used in Brazil and the Far East for the treatment of dysentery and diarrhea. Its main alkaloid, emetine, still constitutes an important drug for amebiasis. The plant which contains the anthelmintic santonin (XL-6) was prescribed under different names by the medicine men of the Hebrews (Jerusalem Oak), Mexicans (Mexican Tea), and Romans (*Chenopodium anthelminticum*). The early explorers found the South American Indians in possession of the cinchona bark from which Pelletier and Caventou extracted the antimalarial alkaloid quinine only three hundred years later (1820). These Indians also chewed coca leaves as a stimulant and euphoric.

Metallic salts were recommended by Hippocrates in the fourth century B.C., and the influence of his teachings was felt for 2000 years in occidental medicine.

The most retarding influence on progressive medicinal thought was exerted by the Roman naturalist Galenus (131–200 A.D.). His contention that herbal mixtures could provide all the essential elements of health, and that proper herb mixtures could thus be used for all conceivable health defects, dominated the middle ages and was fostered by the ecclesiastical monopoly on medical progress which promoted ignorance and superstition among the laiety. The four humors of ancient Greece—heat, cold, moisture, and dryness—were fused with early metallurgical views into a mystical legend which grew as the tendency towards irrationalism rose throughout the first fifteen centuries of Christian civilization. Nevertheless, the history-minded scholar could discern beginnings of a *materia medica* even in those times. In Galenus's apothecary shop (ἀποθήκη, storeroom) herbs and some metallic drugs (copper and zinc ores, iron sulfate, cadmium oxide) were found in abundance, and a semblance of assaying was maintained by insistence on "pure" drugs, that is, the right variety and age of the botanical specimens. Opium, squill, hyoscyamus, and viper toxin were part of Galenus's armamentarium, and an intimation of dosage levels can be seen in his contention that powerful narcotics relieve pain but may also cause death.

The ground-work of chemistry and physics shifted from the Graeco-Roman to the Arabian scene during the next centuries, and in the writings of Arabian alchemists was born the idea of the philosopher's stone. The monk Albertus Magnus (1193?–1280), and his successor Roger Bacon (1214-ca. 1294), amplified this phantom thought and expressed the belief

that the philosopher's stone, if ever discovered, would prove to be a universal remedy or elixir of life. The medical alchemist (iatro-chemist), Paracelsus (1493–1541) adopted the glorification of antimony and its salts in elixirs as cure-alls as they had first been recommended by Basilius Valentinus fifty years earlier. He was so successful in this undertaking that he relegated herbs to a secondary place and made antimony an important though highly controversial drug.

Paracelsus was a reformer but on the whole a superficial quack. The sixteenth century counted a long list of similar figures in many lands who swindled the public with worthless "sympathetic powders", mercury, and the laying on of hands. The latter procedure, an ancestor of psychosomatic medicine, was probably more effective than all the drugs of that era.

Only one great herbal drug of the seventeenth century has survived the test of time, the cinchona bark from which quinine was extracted later. It was brought to Europe from South America by missionaries (hence the name Jesuit bark or powder), and after being rejected initially by unconvinced medical faculties, it became the prize medicine for fevers, chills and malarias, its weight being matched in gold at various times.

The sixteenth and seventeenth centuries saw a perfection of the practices of pharmacists, and the influx of many new drugs of botanical and mineral origin from the New World necessitated a revision and enlargement of older compendia on materia medica. The first pharmacopoeias were edited in Florence (1498), Nürenberg (1535), Basel (1561), Augsburg (1564) and London (1618). These reference works also tried to bring order and reason into the ever-widening gulf between advocates of medicines of herbal and of metallic origin. The latter was to win the uneven battle because the now rapid progress of inorganic chemistry focussed attention on many new substances and made available to the medical profession chemically pure compounds for the first time. It is reasonable therefore to choose the late part of the seventeenth or the early years of the eighteenth century as the beginnings of what we call medicinal chemistry today.[1]

In 1646, the French physician Guy Patin (1602–1672) suggested to a medical student: "Above all flee books on chemistry, *in quorum lectione oleum et perdes.*"[2] This attitude changed as exact laws of chemistry were formulated, as the physiological action of well-defined compounds became amenable to quantitative study, and as the active principles of ancient herbal drugs were extracted, purified and fitted into stoichiometric laws. The transition period was characterized by more precise classifications of botanical drugs and their pharmacodynamic effects, patterned upon the

[1] For a detailed account of ancient and medieval pharmacology, see for example, Mettler, *History of Medicine.* Blakiston, Philadelphia, 1947.

[2] From Packard, *Ann. Med. Hist.*, **1922,** 215.

schemes of Linnaeus (1707–1778) and his followers. In the *Lectures on Materia Medica* by the Scotch surgeon William Cullen (1712–1790), the terms antispasmodic, antiseptic, cathartic, and emetic can be found.[3] But since the action of a drug upon functional organs in the body was not yet understood, the ancient theory of the four humors was unearthed again. Cullen expressed the belief that the neural system was primarily affected by drugs, but that the latter acted differently on persons of different temperaments, the choleric and melancholic, the temperaments of youth and age. He may not have been so wrong in this opinion, as every pediatrician can attest. We also know today that even the most innocuous drug is not tolerated well by some individuals, and this fact has been a justification for the many parallel searches for compounds which might exhibit not a better, but only the same medicinal activity.

Another view of that time was that some drugs acted on fluids, whereas others acted on moving and on static solids in the body. This idea had again its roots in the interpretation of the iatrochemists who had assumed that drugs diluted body fluids or changed its acidity or alkalinity, the change being measured by syrup of violets which, (due to its content of anthocyanins as we now know) turns red in acid, and green in alkaline solution. These contradictory and fluctuating ideas were not aided by the suspicion that chemicals might behave one way in the laboratory and another way in the body, perhaps obeying different laws. This is a forerunner of the observations of many differences of *in vitro* and *in vivo* activities which will be pointed out in virtually every chapter of this book. The explanation of many of these differences is still lacking today. No wonder that eighteenth century medical scientists to whom organic chemistry still was the result of supernatural vital forces should have turned back to mysticism and Graeco-Roman philosophical ideas to explain the action of their drugs.

In the meantime, new medicines were discovered and old ones improved. Withering (1741–1799) introduced digitalis (purple foxglove) as a therapeutic agent for dropsy, and almost the same material is used in the treatment of cardiac edema today. Van Swieten (1700–1772) taught the advantages of corrosive sublimate (mercuric chloride) over older mercurial preparations in "fevers." Ether made its first legitimate appearance in Hoffmann's drops or anodyne (Friedrich Hoffmann, 1660–1742), and opium was dispensed and studied by de Quincey (1785–1859) "to tranquilize all irritations of the nervous system, to stimulate the capacity of enjoyment and . . . to sustain the else drooping animal energies."[4]

[3] Cullen, *Lectures on Materia Medica*. London, 1772.

[4] De Quincey, *Confessions of an English Opium Eater*, in *The Collected Writings of Thomas de Quincey*. Vol. III, 222, Edinburg, 1890.

Van Swieten is generally credited as the founder of the Viennese school of therapeutic nihilism which was more clearly expressed by Hahnemann (1755–1843) and dominated the development of pharmacology and medicinal chemistry until about 1870. Hahnemann believed that "*similia similibus curantur*," that both drugs and spiritual healing powers must be the opposite of the disease, and that only symptoms could be treated, not the cause of the disease. The treatment should consist of diluting drug solutions to the point of practically omitting their content of active components, because high concentrations of drugs produced toxic reactions, *i.e.*, symptoms similar to those of disease. This system became known as homeopathy, and was a major obstacle to the progress of medicinal chemistry since it tended to abolish drugs altogether (therapeutic nihilism). It ran its due course and was finally completely reversed by Pasteur (1822–1895) who regarded *all* disease as caused by pathogenic parasites; this led to the age of healing with chemicals (chemotherapy).

Another theory was proposed by Samuel Thomson (1769–1843) in this country who stated that "all diseases are the effect of one general cause and may be removed by one general remedy."[5] Echoes of this statement are found in Ehrlich's life-long ambition to find the *materia magna sterilans*, a cure-all for all infectious diseases. The nearest approach to this description of a drug may be found in the modern antibiotics, penicillin and aureomycin.

Perhaps the most beneficial medicinal innovation of the nineteenth century was the discovery of general anesthesia. Davy (1778–1829) introduced nitrous oxide (laughing gas) as an inhalation anesthetic, and this was followed by the first clinical experiments with ether in the surgical amphitheater. Crawford W. Long (1815–1878) of Georgia employed ether as an anesthetic in 1842, and William T. G. Morton (1819–1868) of Boston showed its use in the operating room at Massachusetts General Hospital in 1846. The British anesthetist Simpson (1811–1870) employed chloroform the following year, and surgery was put on a scientific basis by these agents.

The first important pharmacodynamic agents to be isolated in pure form were alkaloids several of which were extracted from long-known sources in the first 75 years of the nineteenth century. Morphine was isolated by the pharmacist Sertüner in 1806, the mydriatic base atropine by Mein, Geiger and Hesse in 1833, and quinine by Pelletier and Dumas in 1823. Early synthetics included acetanilide, salicylic acid (Kolbe, 1818–1884), antipyrine (Knorr, 1883), aspirin (Dreser, 1899), and diethyl barbiturate (Emil Fischer and Mering, 1903). In the early 1880's one of the greatest practitioners of medicinal chemistry, Paul Ehrlich (1854–1915)

[5] Thomson, *The Thomsonian Materia Medica, or Botanic Family Physician*. 12th ed., New York, 1841, p. 505.

laid the foundations to chemotherapy. At the turn of the century Stolz synthesized the first hormone (Adrenaline, 1904), and Barger and Dale made in 1909 a fundamental study of the effect of chemical structure in the series of sympathomimetic amines upon the physiological effects of these compounds. This field underwent a renaissance after the discovery of the analeptic properties of ephedrine by K. K. Chen (1923), and his study stimulated an enormous upsurge in varied pharmacodynamic investigations.

The successful theories of Ehrlich concerning the distribution and mode of action of drugs, and his great work on arsenical compounds were an enticing invitation for further explorations of chemotherapy. Since individual investigators could barely hope to initiate and conclude a complete study of a drug single-handedly, they became partners in research teams composed of experts in all branches of the sciences concerned. The best coordination for such teams was found in the pharmaceutical industry, and many great developments from 1910 on have taken place in industrial laboratories. The trypanocidal drug Suramin, the antimalarials pamaquine and quinacrine, the twenty-odd antihistaminic drugs now in use, the antibacterial sulfonamide drugs and many others have been developed in this manner. The word "developed" has been chosen with care since the basic concepts of these drugs have always originated in the minds of individual investigators, but the patient variations of conditions, structures, testing and production methods have become the task of team work. This is also reflected in the great discoveries of Domagk (sulfonamides, surface-active ammonium antiseptics, antitubercular thiosemicarbazones), of Fleming and Waksman (penicillin, streptomycin), of Miescher (Nupercaine, doisynolic acids, Antistine) and of Kendall and Hench (Cortisone), which would not have become practical realities without industrial research coordination.

As new ideas have attempted to unify medicinal-chemical thought, it has always been necessary to test their value by many examples. The metabolite-antagonist theory of drug action, for instance, obtained its practical start by the discovery of Woods and Fildes that sulfanilamide antagonized *p*-aminobenzoic acid, and that the quantitative aspects of this relationship could serve as an explanation of the bacteriostatic activity of sulfanilamide. This attractive theory has been found applicable in countless other cases, and its ramifications have shown that a fundamental explanation of the mode of action of perhaps all drugs has been found here. Yet, the practical fruits of this theory have been singularly disappointing, and the man-power of industrial scientific laboratories has again helped to furnish the many examples which have given us a more adequate perspective in this field.

No attempt will be made in this chapter to give a full account of recent discoveries, theories and achievements of medicinal chemistry. The reader will find pertinent data in the individual chapters of this volume, and correlations of data in those sections of the book which are devoted to the theory of our subject. In Table I, the most significant of these data may be found listed in chronological order.

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TABLE I. SOME IM

TABLE I. SOME IMPORTANT DATES IN THE DEVELOPMENT OF MEDICINAL CHEMISTRY DURING THE LAST HUNDRED YEARS

Year	Discovery or observation	Investigators	Reference[a]
1850	Iodides recognized as dietary prevention of goiters	Chatin	XXVI
1853	Bromides used as sedatives in epilepsy; 1864 as hypnotics	Laycock; Behrend	X
1856	Adrenal secretion found to raise blood pressure	Vulpius	XIX
1867	Phenol is introduced as antiseptic in surgery	Lister	XLIII
1868	Tetraethylammonium salts have curare action	Brown and Fraser	XXII[14]
1869	Hypnotic activity of alcohols increases in proportion to their molecular weight	Richardson	IX[13]
1869	Hypnotic action of chloral hydrate is discovered	Liebreich	IX
1874–5	Nitrites have vasodilator activity	Bernheim, 1874; Mayer and Friedrich, 1875	XIII
1876	Salicylic acid found to have analgetic properties	Stricker	XI
1877	Isolation of anthelmintic alkaloid pelletierine from pomegranate	Tanret	XL
1879	Iodoform is introduced as wound antiseptic	Mosetig	XLIII
1881	Mercuric chloride is shown to kill anthrax bacillus	Koch	XLIII[24]
1882	Paraldehyde first used as hypnotic	Cervello	IX
1883	Antipyrine is synthesized and introduced as fever agent	Knorr	XI
1884	Bacterial classification based on staining properties	Gram	XXXIII[1]
1884	Local anesthetic action of cocaine is recognized	Köller	VIII
1885	Mercurous chloride is used as diuretic	Jendrassik	XV[10]
1885	Side-chain theory of drug action is announced	Ehrlich	XXXIII[5]
1886	Salol is introduced	Nencki	XI[70]
1886	First use of acetanilide as analgetic-antipyretic	Cahn	XI[65]
1887	Acetophenetidine is introduced	Hinsberg	XI[66]
1887	Ephedrine is isolated from *Ephedra vulgaris*	Nagai	XIX[22]
1888	Sulfonal is used as a hypnotic	Baumann and Kast	IX[22]
1888	Diuretic properties of caffeine discovered	Schröder	XV[5]
1889	Creosol is recommended as an expectorant	Fraenkel	XVIII
1890–1900	Resistance to drugs is studied	Ehrlich	VI
1891	Castor oil owes its cathartic activity to ricinoleic acid	H. H. Meyer	XVII

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1891	The term chemotherapy is coined	Ehrlich	XXXI[1]
1891	Methylene blue is used in malaria	Ehrlich	XXXIII
1895	Hexamethylenetetramine is found to have antiseptic properties in acidified urine	Nicolaier	XLIII
1897	The Eucaines are tested for local anesthetic activity	Harries	VIII[3]
1897	Ross finds malaria is transmitted by female Anopheles mosquito		XXXV
1898	Cathartic properties of phenolphthalein are discovered		XVII
1899	Aspirin is introduced as mild analgetic and antipyretic	Dreser	XI[71]
1899–1901	Theory of lipid-water distribution as basis of explanation of anesthesia is advanced	Overton-Meyer	VII[1]
1900	Benzocaine is introduced as local anesthetic	Einhorn	VIII
1900	Caffeine is synthesized	Traube	XII[15]
1902	The use of theophylline as diuretic is advocated	Minkowsky	XV[5]
1902	Adrenalin is purified	Abel, Fürth, Takamine	XIX[13]
1903	Phenol coefficient of antiseptics is established	Rideal and Walker	XLIII[2]
1903	Veronal is introduced as first barbiturate hypnotic	Emil Fischer and v. Mering	IX[1]
1904	Atoxyl is tried in experimental trypanosomiasis	Thomas and Breinl	XLI
1904	Iodinated 8-hydroxyquinolines are tested in amebiasis; previously tested clinically (Schenzinger, 1893), synthesized by Claus (1892)	Küster	XXXVII
1904	Procaine is synthesized and introduced as local anesthetic	Einhorn	VIII[6]
1904	Epinephrine is synthesized	Stolz	XIX[16]
1906	Acetylcholine is synthesized and its vasodepressor effect studied	Hunt and Taveau	XIX
1906–7	The pharmacology of the ergot alkaloids as adrenergic blocking agents is investigated; (the first ergot bases were isolated by Tanret, 1875–1879)	Barger, Carr, and Dale	XX[2]
1907	Trypan red is found to kill trypanosomes which cause Mal de Cadras	Ehrlich	XXXIII[6]
1908	Cinchophen is introduced for gout and arthritic pain	Nicolaier and Dohrn	XI

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

Year	Discovery or observation	Investigators	Reference[a]
1908	Colchicine is shown to be effective in leukemia	Dixon and Malden	XXVII
1908	Synthesis of sulfanilamide, but its bacteriostatic activity remains unknown	Gelmo	XXXIV[7]
1909	Arsphenamine is synthesized	Ehrlich and Bertheim	XLI
1909	Trypan blue is found active in Babesia	Nuttall and Hawden	XXXIII[7]
1909	Epinine is recommended as uterine stimulant	Pyman	XIX[58]
1909	Systematic investigation of sympathomimetic amines is carried out	Barger and Dale	XIX[9]
1910	Acetarsone tested in syphilis and yaws; this drug was reinvestigated as Stovarsol by Fourneau (1921)	Ehrlich and Hata	XLI
1910	The vasodilator activity of histamine is discovered	Barger and Dale	XXIV[1]
1910	Anthiomaline studied for use in trypanosomiasis; Brown (1944) found use in filariasis	Thomson and Cushny	XXXVII
1911	The term "vitamin" is coined	Funk	XXVIII
1912	Introduction of Neoarsphenamine	Ehrlich	XLI
1912	Phenobarbital is used in epilepsy	Fischer and Mering	X
1912	Pyridium is synthesized and used as urinary antiseptic	Ostromislensky	XXXIII
1912	Acriflavine is active in trypanosomiases	Benda	XXXIII[14]
1913	Proflavine is shown to be antibacterial	Browning	XXXIII[15]
1913	Emetine is found to destroy *Endamoeba histolytica*	James	XXXVII
1914	Gentian violet is employed as antiseptic	Churchman; Russel	XL[23]
1914	Classification of nervous systems as cholinergic and adrenergic	Dale	IX[2]
1915	Histamine is recognized as cause of anaphylaxis	Mann; Cannon (1918); Best (1927)	XXIV[2]
1916	Germanin first tested as trypanocidal agent in human sleeping sickness	Roehl; formula published by Fourneau, 1923	XXXVII
1916	Heparin is found to prolong blood clotting time	McLean and Howell	XVI[2, 3]
1917	Hypochlorites and chloramines used as antiseptics	Dakin	XLIII[11]
1919	Tryparsamide first tested in trypanosomiases	Jacobs and Heidelberger	XL
1919	Antiseptic activity of Mercurochrome is reported	Young	XLIII

Table continued

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1919–1920	Relation of structure to mydriatic and antispasmodic action of atropine is studied	Cushny	XXIII
1920	Synthesis of ephedrine is accomplished	Späth	XIX[21]
1920	Dilaudid and Dicodid are synthesized	Freund	XI[15]
1920	Organic mercurials are studied as diuretics	Saxl and Heilig	XV[11]
1921	Rivanol is found to be bacteriostatic	Morgenroth	XXXIII[19]
1921	Acetylcholine is recognized as mediator of nervous transmission	Loewi	XIX[1]
1922	Fuadin (Stibophen) is used in leishmaniasis, granuloma venereum, bilharzia	Khalil	XLI
1922	Insulin is purified; crystalline insulin by Abel (1926)	Banting and Best	XXIX
1922	Coramine synthesized and tested as analeptic	Ciba Laboratories	XII
1923	Ephedrine studied pharmacologically	Chen and Schmidt	XIX[22]
1923	Avertin is synthesized for use as anesthetic	Willstätter	VII[14]
1923	Unsymmetrically substituted dialkylbarbituric acids are shown to be valuable hypnotics	Shonle	IX[2]
1923	Rules governing the relation of structure to hypnotic activity of barbiturates are evolved	Shonle; Dox	IX[5]
1923	Physostigmine is recognized as inhibitor of cholinesterase	Barger and Stedman	XXI[31]
1926	Avian malaria tests are published	Roehl	XXXV[1]
1926	Pamaquine is synthesized and introduced as gametocidal antimalarial	Schuleman, Schönhöfer and Wingler	XXXV[47]
1926	Metrazol is synthesized; used as convulsant	Schmidt	XII[9]
1926–1940	Experimental carcinogenesis with polycyclic hydrocarbons and related products is studied	Cook; Fieser	XXVII
1927	Thyroxine is synthesized	Harington and Barger	XXVI[4]
1927	Benzedrine is found to have vasopressor and centrally stimulating effects; the base is used in inhalers as nasal shrinker (Nabenhauer, 1932)	Alles	XIX[40]

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

[a] By chapter and footnote number.

Year	Discovery or observation	Investigators	Reference[a]
1927–8	Ascorbic acid is isolated from adrenals, oranges, cabbage	Szent-Györgyi; Zilva	XXVIII
1927	Neosynephrine used as local vasoconstrictor	Ehrisman; Tainter (1930)	XIX[29]
1928	Isolation of natural estrogenic hormones is started	Butenandt; Marian; Doisy	XXIX
1929	Mustard gas is shown to inhibit growth of tumors	Berenblum	XXVII[25]
1929	Propadrine is prepared as vasopressor	Hartung and Munch	XIX[31]
1929	Penicillin is suspected among metabolic products of *Penicillium notatum*	Fleming	XXXVIII[8]
1921–1931	Vitamin D_2 (Viosterol, Calciferol) is obtained from irradiated ergosterol	Windaus; Rosenheim; Reerink and van Wijk	XXVIII
1929–1931	Concept of isosterism in medicinal chemistry is formulated	Grimm; Erlenmeyer	IV
1930	Structure of the anthelmintic agent, santonin, is elucidated	Clemo	XL[12]
1930	Cyclopropane is first used as general anesthetic	Henderson and Luckhardt	VII[10]
1930	Divinyl ether is used as general anesthetic; synthesis by Ruigh and Major	Leake and Chen	VII[7]
1931	Prostigmin is prepared as inhibitor of cholinesterase	Aeschlimann	XXI[35]
1931	Picrotoxin is introduced as analeptic in barbiturate poisoning	Tatum	XII
1931	*n*-Hexylresorcinol is recommended as anthelmintic	Lamson	XL[9, 10]
1931	Neostibosan is tested in leishmaniasis	Uhlenhut, Hügel, and Seifert	XLI
1932	Carbarsone is found effective in amebiasis	Leake	XXXVII
1932	Respiratory enzyme is found to contain riboflavin	Warburg	XXVIII
1932	Nupercaine is employed as long-lasting local anesthetic	Miescher	VIII[2]
1932	Mecholyl, Carbamylcholine and other cholinergic drugs are tested	Major and Cline; Kreitmair	XXI[10, 12]
1932	Modern methods of testing of analgetic agents are developed	Eddy (1932)	XI[7]
		d'Amour and Smith (1941)	XI[9]
		Hardy and Wolff (1940)	XI[10]
1932	Benzodioxane derivatives as sympatholytics	Fourneau	XX[10]
1932	Malaria in monkeys used as test for antimalarials	Knowles	XXXV[3]
1932	Atebrine is introduced as synthetic schizonticidal agent	Mietzsch and Mauss	XXXV[58]
1932	Prontosil is prepared and tested; proves to be first antistreptococcal agent	Mietzsch, Klarer, Domagk	XXXIV[2, 3]

Table continued

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1933	Ascorbic acid is synthesized	Reichstein; Haworth	XXVIII
1933	Estradiol is prepared by partial synthesis	Schwenk; Girard	XXIX[24]
1933	Paredrine is developed as non-analeptic vasopressor	Alles	XIX[52]
1934	Progesterone is synthesized from cholesterol	Butenandt	XXIX[54]
1934	Androsterone is synthesized from cholesterol	Butenandt; Ruzicka	XXIX[4]
1934	Plasmocid tested as antimalarial	Strukov	XXXV[45]
1934	Phenothiazine is introduced as insecticide, then as anthelmintic in veterinary medicine (1939)	Haller; McNaught, Beards, and Eds	XXXVIII[29, 30]
1934	Chlorazodin is synthesized as bactericidal agent	Schmelkes	XLIII[18]
1934	Mapharsen is found to be highly effective in syphilis	Tatum	XLI
1935	Germicidal quaternary ammonium salts are discovered	Domagk	XLIII[48]
1935	Aromatic diamidines are found effective in trypanosomiases and schistosomiasis	Lourie and Yorke	XXXVII
1935	Mandelic acid derivatives are used as antiseptics	Rosenheim	XXXVIII
1935	Thiamine is synthesized	Williams; Andersag and Westphal	XXVIII[7]
1935	Partial synthesis of testosterone is recorded	Butenandt; Ruzicka	XXIX[64]
1935	Sex hormone therapy of cancers is instituted	Loeb	XXVII[9]
1935	Sulfanilamide is recognized as bacteriostatic drug	Tréfouël, Tréfouël, Nitti and Bovet	XXXIV[4]
1935	Theory of anthelmintic action is proposed	Rosenmund	XL[21]
1935	Prostigmin is recognized as most effective drug in myasthenia gravis	Mary Walker	XXI[36]
1935	Iodinated organic compounds are used as radiopaques	Binz	XXV[2]
1935–1936	Thiobarbiturates are tested as central and spinal anesthetics	Tabern and Volwiler, Miller, Munch, Crossley and Hartung	IX[9, 10]
1936	Vitamin P is found necessary in certain hemorrhagic conditions	Szent-Györgyi	XXVIII[24]
1936	Vitamin D_3 is isolated from tuna oil	Brockmann	XXVIII[28]
1936	Tocopherol: Discovery and isolation	Evans, 1936	
	Structural proof	Fernholz, 1938	
	Synthesis	Karrer, L. I. Smith, Todd, 1938	XXVIII
1936	Structure of cozymase elucidated	Euler	XXVIII

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

Year	Discovery or observation	Investigators	Reference[a]
1936	Synthesis of riboflavin is accomplished	Kuhn; Karrer	XXVIII[10]
1936	Trasentin is introduced as antispasmodic	Meier	XXIV[27]
1936	Metopone is synthesized and found to be a powerful analgetic	Small; Eddy	XI[18, 19]
1936	Mode of action of morphine is discussed: cholinergic? adrenergic?	Bernheim Pero (1939)	XI[22] XI[23]
1937	Vitamin A is synthesized	Kuhn	XXVIII
1937	Niacinamide is recognized as pellagra-preventing factor	Elvehjem	XXVIII
1937	Curare is tested as muscle relaxant	Rosenblueth	XX[2]
1937–9	Early antihistaminic agents are developed	Bovet and Staub	XXIV[16, 17]
1937	Hydantoins are introduced as anticonvulsants	Putnam and Merritt	X[2]
1937	The insecticidal action of DDT is discovered, and the agent is applied to exterminate insect vectors of infectious diseases	Müller	XXXV
1938	Sulfapyridine is used in bacteremias	Whitby	XXXIV[9]
1938	Sestron shows antispasmodic properties as predicted from its structure	Rosenmund	XXIII[14]
1938	Simple fatty acids are found to be fungistatic	Peck	XXXIX[4]
1938–9	Stilbestrol and Hexestrol are prepared based on structural analogies to estrogenic hormones	Dodds	XXIX[37, 38]
1939	The structure of pantothenic acid is elucidated	R. J. Williams	XXVIII[14]
1939	Synthesis of pyridoxine is reported	Kuhn; Harris and Folkers	XXVIII[13]
1939	Sulfathiazole is synthesized	Fosbinder and Walter	XXXIV[11]
1939	Demerol is synthesized and introduced as analgetic	Eisleb and Schauman	XI[37]
1939	Erythrina alkaloids are studied as muscle relaxants	Folkers	XXII
1939	Priscoline is found to act as short-lasting vasodepressor	Hartman and Isler	XIX[60]
1939	Vitamin K_1 and K_2 are discovered and their function is studied	Dam; Karrer; Doisy	XXVIII
1939	Antihemorrhagic activity of Menadione is established	Ansbacher and Fernholz	XXVIII
1939	The biosynthesis of thyroxine is explained	Harington	XXVI[11]
1939	Vitamin K: structure is established, synthesis accomplished	Dam, Karrer, Doisy, Almquist, Fieser	XXVIII[44]

Table continued

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1940	Monoamine oxidase is recognized as the primary enzymatic deactivator of phenethylamines	Beyer	XIX[76]
1940	Furmethide is used in glaucoma	Fellows and Livingston	XX[26]
1940	Sulfaguanidine is shown to be a useful bacteriostatic in intestinal infections	Winnek	XXXIV[19]
1940	Sulfadiazine is found highly effective and relatively non-toxic bacteriostatic agent	Roblin, Williams, Winnek and English	XXXIV[15]
1940	The antimetabolite theory of drug action is proposed	Woods and Fildes	XXXIV[38]
1940	Pantothenic acid is synthesized	Folkers; Reichstein; Kuhn	XXVIII[15]
1940	Synthesis of desoxycorticosterone from steroid materials is announced	Reichstein	XXIX[77]
1940	Manufacture of penicillin starts	Chain, Florey; Moyer	XXXVIII[10, 11]
1941	Tyrothricin is isolated from *Bacillus brevis*	Dubos and Hotchkiss	XXXVIII[81]
1941	*p*-Aminobenzoic acid is shown effective in rickettsias	Ansbacher	XXVIII[21b]
1941	Promine (synthesized in 1937 by Tillitson) is tested in experimental tuberculosis	Feldman and Hinshaw	XXXVI[58]
1942	The structure of biotin is elucidated	du Vigneaud	XXVIII[19]
1942	Quinonoid hypothesis of antimalarial action of quinoline derivatives is proposed	Schönhöfer	XXXV[42]
1942	Bacteriostatic activity of sulfa drugs is shown to be related to their pK_a	Bell and Roblin	XXXIV[47]
1942	Phthalyl- and succinylsulfathiazole are recommended for intestinal bacteremias	Moore and Miller	XXXIV[14]
1942	Neoantergan is shown to be effective antihistaminic agent	Halpern	XXIV[28]
1943	Benadryl is first American antihistaminic drug	Rieveschl	XXIV[20]
1943	Dexedrine is prepared as potent central stimulant	Nabenhauer	XIX[41]
1943	Pavatrine is proposed as antispasmodic	Burtner and Cusic	XXIII[45]
1943	Biotin is synthesized	Harris, Wolf, Mozingo & Folkers	XXVIII[20]
1943	Dienestrol is shown to be highly estrogenic	Short	XXIX[49]

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

Year	Discovery or observation	Investigators	Reference[a]
1943	Dicoumarol is established as anticoagulant in sweet clover hay	Link	XVI[7]
1943	Diasone is tested in experimental tuberculosis	Raiziss	XXXVI[59]
1943	Sulfamylon (Marfanil) is used in Gram-negative bacteremias	Klarer	XXXIV
1943	10-Aminoacridine is found non-resistance forming moderately effective bacteriostatic agent	McIntosh	XXXIII[20]
1944	Streptomycin is isolated from *Actinomyces griseus*	Waksman	XXXVIII[45]
1944	Sulfaquinoxaline is introduced for the treatment of coccidiosis in fowl	Tishler	XXXIV[18]
1944	Phenylpantothenone is found to antagonize plasmodial requirements of pantothenic acid	Woolley	XXXV[70]
1944	Melarsen oxide is useful in African trypanosomiasis	Banks	XLI
1944	Estrogenic activity of doisynolic acids is discovered	Miescher	XXIX[29]
1944	Tridione is prepared as antiepileptic drug	Spielman	X[11]
1944	Polyvinylpyrrolidone is used in parenteral fluid therapy	Reppe	XIV
1944–6	Thiouracil is found to inhibit thyroxine synthesis in gland	Roblin; Astwood	XXVI[24]
1945	Structure of penicillin is published		XXVIII
1945	The synthesis of quinine is announced	Woodward and Doering	XXXV[9]
1945	The synthesis of methadon is divulged	Bockmühl and Schaumann	XI[48]
1945	Promizole is found effective in acid-fast infections	Bambas	XXXVI[60]
1945	Derivatives of 1,2-diphenylethanolamine are tested as tumor necrotizing agents	Hartwell, Shear	XXVII[21]
1945	Phenergan is shown to have powerful antihistaminic action	Halpern	XXIV[40]
1945	BAL (Dimercaprol) is used as antidote for arsenic and metal poisoning	Peters; Stocken	XXXII[63]
1945	Pteroylglutamic (folic) acid; structure is proved and synthesis carried out	American Cyanamid Company Laboratories	XXVIII
1945	Plasmodia are cultured *in vitro*	Ball; Berliner	XXXV[4, 5]
1945	Hetrazan is developed as antifilarial drug	Lederle Laboratories	XXXVII
1946	Paludrine is synthesized and found to be suppressive in vivax and falciparum malaria, and prophylactic in the latter	Curd and Rose	XXXV[76]

Table continued

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1946	Chloroquine is found to be an excellent suppressive agent in vivax malaria	Drake; Winthrop-Sterling Co.	XXXV[53]
1946	*p*-Acetamidobenzaldehyde thiosemicarbazone is tested in 5000 cases of tuberculosis	Behmisch and Domagk	XXXVI[63]
1946	*p*-Aminosalicylic acid is found to be clinically useful tuberculostatic agent	Lehman	XXXVI[55]
1946	Dibenamine causes adrenergic blockade	Nickerson and Goodman	XX[18]
1946	Morphinan is synthesized and shown to be about as active as morphine	Grewe	XI[5]
1946	Benzestrol proves to be a potent estrogen	Stuart	XXIX[51]
1946	Estrone is synthesized	Anner and Miescher	XXIX[33]
1946–1948	Cortisone is synthesized	Sarrett; Kendall, Mason and Mattox; Julian; Gallagher	XXIX[76]
1946	Panpartit is shown to have antispasmodic effect in Parkinsonism	Weston; Tilford, Van Campen, Shelton	XXIII[52]
1946	Pyribenzamine is released as antihistaminic agent	Huttrer, Djerassi and Scholz	XXIV[29]
1946	Antistine is recommended as antihistaminic drug	Miescher	XXIV[37]
1946	Chlorothen is prepared as antihistaminic	American Cyanamid Company	XXIV[35]
1946	Diisopropyl fluorophosphate is recognized as inhibitor of cholinesterase	McCombie and Saunders	XXI[45]
1946	Myanesin is used as muscle relaxant in spastic states	Berger	XXII[25]
1946	Urethan is tested in leukemia	Paterson; Haddow	XXVII[27]
1946	Aureomycin is isolated from *Streptomyces aureofaciens*	Duggar	XXXVIII[66]
1946	Penicillin is synthesized	du Vigneaud	XXXVIII[17]
1947	Carinamide can maintain penicillin blood levels by selective kidney blockade	Beyer	XXXVIII[24]
1947	Isuprel is recommended as bronchodilator	Lands	XIX[65]
1947	Pentaquine is released as effective antimalarial	Elderfield	XXXV[50]
1947	The therapeutic mechanism of certain dyes depends on inhibition of the conversion of glutamic acid to peptides	Gale	XXX[9]

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

Year	Discovery or observation	Investigators	Reference[a]
1947	Bacitracin is isolated from *Bacillus subtilus*	Meleney	XXXVIII[77]
1947	Chloromycetin (Chloramphenicol) is isolated from *Streptomyces* strains	Burkhalter	XXXVIII[69]
1947	Miracil is found effective in schistosomiasis	Wood	XXXVII
1947	Podophyllin is tested as tumor necrotizing agent	Hartwell	XXVII[24]
1947	Dehydrocorticosterone is synthesized	Wettstein and Meystre	XXIX[78]
1947–1948	Structure of streptomycin is elucidated	Folkers; Carter; Wolfrom; Wintersteiner	XXXVIII
1948	Camoquine is found to be a valuable suppressive in falciparum malaria	Burckhalter	XXXV[79]
1948	Naphthoquinone derivatives are announced to have antimalarial activity	Fieser	XXXV[71]
1948	Benzedrex is chosen as non-analeptic nasal shrinker	Ullyot, Fellows	XIX[43]
1948	Phenylacetylurea, a segment of the molecule of phenobarbital, is useful in petit mal epilepsy	Spielman	X[4]
1948	Theories about spatial influences on muscarinic action of cholinergic drugs are proposed	Pfeiffer; Ing	XXI[53, 56]
1948	Khellin is shown to be a coronary vasodilator	Anrep	XIII
1948	Antabuse is proposed as drug for allay of alcoholism	Jacobsen	XVII[5]
1948	Neohetramine is introduced as antihistaminic drug	Friedman	XXIV[32]
1948	Thephorin is recognized as antihistaminic agent	Roche Co.	XXIV[45]
1948	Chlorotrimeton is found to be powerful antihistaminic drug	Schering Co.	XXIV[44]

Table continued

TABLE I (*continued*)

Year	Discovery or observation	Investigators	Reference[a]
1948	Commercial method of synthesizing papaverine is divulged	Eli Lilly & Co.	XXIII[2]
1948	Aminopterin is tested successfully in leukemia	Farber et al.	XXVII[29]
1949	Modified penicillins are prepared by additives in fermentation	Eli Lilly & Co.	XXXVIII[18]
1949	The term chemotherapy undergoes a change of meaning	Roblin	XXXI[2]
1949	Chloromycetin is synthesized commercially	Parke, Davis & Co.	XXXVIII[73]
1949	Cortisone is used in rheumatoid arthritis	Kendall, Hench	XXIX[72]
1949	The goitrogenic principle of cabbage and kale is isolated	Astwood	XXVI[21]
1949	Vitamin B_{12} is isolated	Smith, Parker; Folkers	XXVIII[22]
1949	Adenosine triphosphate is shown to have cardiotonic activity	Szent-Györgyi	XIII[1]
1949	Banthine is shown to have favorable effects in peptic ulcer	Cusic and Robinson	XXI[24a]
1949	Anthrycide curative in trypanosomiasis of cattle	Curd and Rose	XXXVII
1950	Terramycin is isolated and studied	Finlay; Keefer	XXXVIII[75]

[a] By chapter and footnote number, as XXII[14] (chapter XXII, footnote 14).

CHAPTER III

Relation of Chemical Structure and Biological Activity

In the course of the nineteenth century, many natural products were isolated and purified, and their chemical structure was determined. A few of them exhibited medicinally useful properties, and from the pharmacological investigation of many others some ideas about toxicity and physiological specificity could be derived. It soon became apparent that certain structural units of the molecules of biologically active compounds are to be found also in other substances having similar properties, and this observation was seized upon as the only available guiding thought for further researches. The modification of the structure of a promising compound is still the main line of approach to new drugs. It holds forth the hope that suitable structural variation may increase the therapeutic usefulness of a given type of compound by widening the differences between desirable actions and the toxicity syndrome. Structural variations bring about new physical properties, and apart from decreasing the toxicity of a compound, improvements in solubility, volatility, color, odor, etc., may widen the utility of a given drug. Moreover, even a very minor change in the chemical structure may uncover physiological properties which had been dormant, or overshadowed by toxic side-effects in the parent compound.

The ideas about relations of structure and activity underwent several changes as knowledge of the chemical and physical properties of matter expanded. Many generalizations, originally accepted as truths, had to be narrowed to a limited series of drugs as details of fine differences were explained as expressions of new mechanisms. On the other hand, the hope has never been abandoned that the action of different drugs might be explained on a unified basis. The Sections dealing with isosterism, and with interference of drugs with enzyme systems will furnish examples of such trends.

Even the most advanced, and most carefully considered theories have not revealed regularities in the relation of chemical structure to physiological action which could be used indiscriminately in one series of compounds after proving their value in another one. Leaving aside inorganic compounds with their widely divergent effects on living cells, pronounced regularities could be expected, at least in series of simple closely analogous compounds. This is actually the case in homologous series.

I. RELATIONS IN HOMOLOGOUS SERIES

In some homologous series, such as the hypnotic α-bromo amides ($RCHBrCONH_2$) and the antiseptic 4-alkylresorcinols (1,3-$(HO)_2C_6H_3$-4-R), the lowest members show very little activity. Lengthening of the carbon chain to 5–9 atoms causes an increase in pharmacological effects but further lengthening brings about a sudden decrease. On the other hand, the antiseptic power of simple aliphatic aldehydes is greater for the lower than for the higher members of a homologous series of such compounds. There, the lower aldehydes are chemically toxic agents while the higher ones act purely physically.

Careful studies have been made in homologous series of general cell depressants which can be classified both as toxic, and as narcotic substances. Toxicity and narcosis are intimately connected wherever the latter is considered as a depressant effect on a cell rather than the stupefying syndrome observed in animals. Narcotics are toxic drugs which act by virtue of their whole molecule; volatile anesthetics, for example, are exhaled unchanged and must act therefore by their physical action on cell constituents only.

Physical adsorption is undoubtedly the first step in any biological reaction between drugs and cell chemicals. The action of narcotics is explicable partly by their adsorption to cell structures, solution in the lipids, or the coagulation of cell proteins under these conditions. The primary process of adsorption is reversible, as seen in the termination of anesthesia as soon as the anesthetic has been excreted. The irreversible effects leading to the death of the organism must be due to secondary processes, perhaps deep changes of solubilities and adsorption rates which disorganize all normal chemical reactions within the cell.

In many experiments with narcotics the equitoxic concentrations have been measured either in aqueous solutions in which the cells or organs to be influenced were immersed, or, in the case of fumigants, in the gaseous atmosphere surrounding the organism. Only in few instances has the toxic concentration been measured in the cells directly affected by the poison. The first members of homologous series show, therefore, approximately the same "toxicity" as measured by the equitoxic concentrations in the external phase. As one goes up the series, "toxicity" decreases since chemical reactivity declines. As soon as physical toxicity becomes predominant, equitoxic concentrations of succeeding members will drop rapidly, approximately by a factor of three with each additional carbon atom.[1] That means, intensity of action increases with chain length, the logarithm of the equieffective (equitoxic, equinarcotic, equiantimalarial) concen-

[1] **Ferguson,** *Proc. Roy. Soc.*, **127,** 387 (1939).

tration being a linear function of the number of carbon atoms. However, this does not go on forever. Sooner or later a homologous member is reached with has the maximum activity, and beyond it one encounters a "cut-off," the next member having barely any or no activity. The position of the cut-off depends on the homologous series, on the nature of the biological action, and even on such factors as the relative resistance of different strains of the same organism.

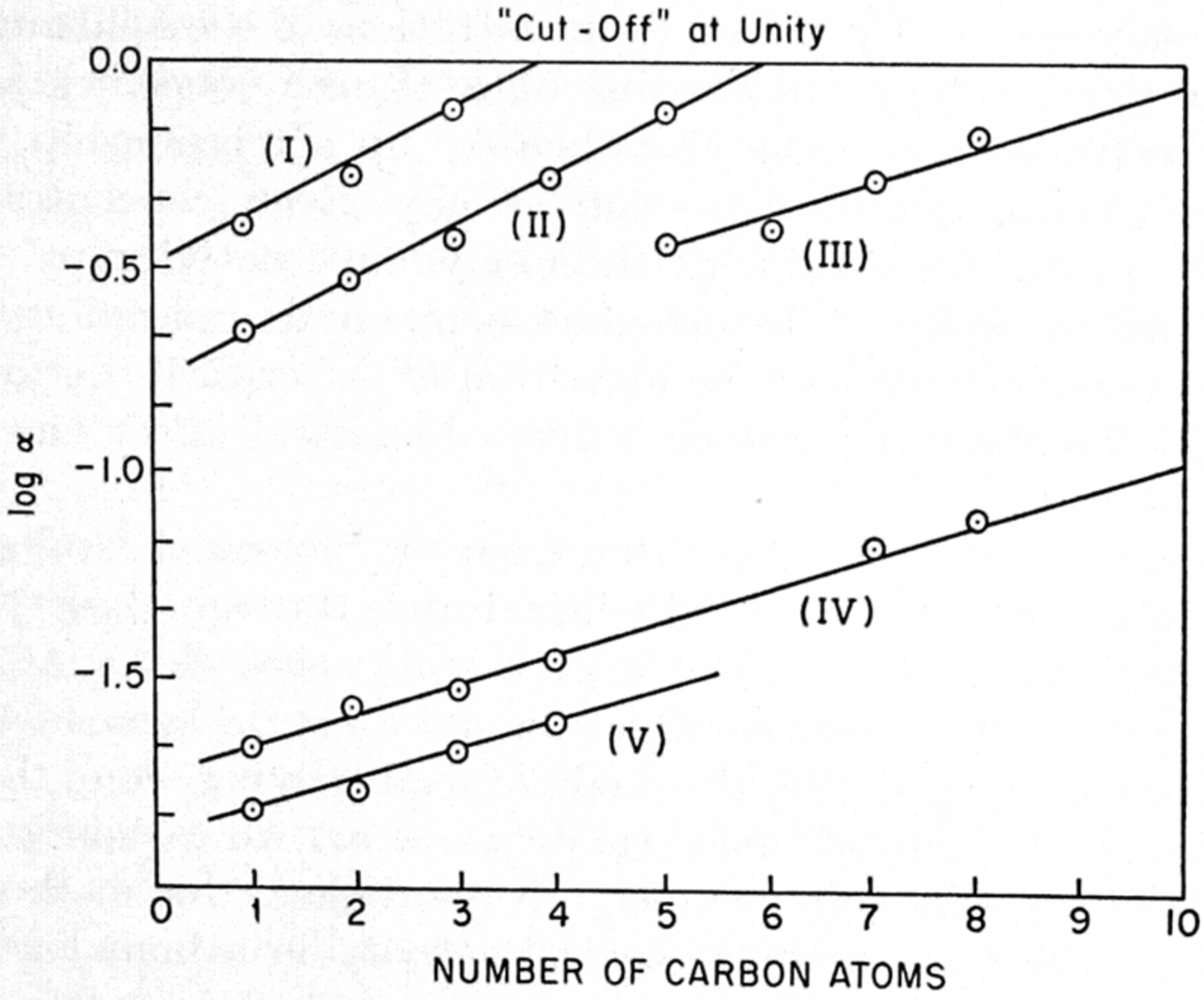


Figure 1. Relation of Number of Carbon Atoms in Homologous Series to Thermodynamic Activity (α).[4] See text, page 30.

Homologous series	*Biological effect tested*
I. Alkyl acetates	Hemolysis of blood
II. Alcohols	Bactericidal action, *Staphylococcus aureus*
III. Paraffins	Narcosis of mice
IV. Alcohols	Inhibition of development of sea urchin egg
V. Alcohols	Narcosis of tadpoles

It is possible to predict the position of the highest active member of a homologous series from the results obtained with lower homologs.[2] This can be achieved if, instead of the actual concentrations of homologs which can bring about the same biological effect, their effective concentration (thermodynamic activity) is used.[3] This factor represents the really us-

[2] Shaffer and Tilley, *J. Bact.*, **14,** 259 (1927). Badger, *Nature*, **158,** 585 (1946).
[3] Lewis and Randall, *Thermodynamics*. McGraw Hill, New York, 1923, Chapter 22.
[4] From Badger, *Nature*, **158,** 585 (1946).

able concentration, leaving aside the percentage of the solute which is inactivated physically by association and other field forces of its ionic atmosphere. It is calculated from the actual concentration (c) by the equation:

$$\alpha = f \times c$$

where α is the thermodynamic activity and f is the activity coefficient.

One can determine thermodynamic activity by measuring the depression of the freezing point, the elevation of the boiling point, or changes in osmotic pressure caused by different concentrations of the solute in question. From these values, the corresponding data at zero concentration can be plotted by extrapolation. One can then set up a relationship to, for instance, the freezing point depression at any given concentration, and that will be in the same ratio as thermodynamic activity to concentration. In twelve series of homologous compounds (paraffins, alcohols, esters) the average increase of the logarithm of the critical thermodynamic activity which suffices to produce a given biological effect has been calculated to be 0.10.

If one can calculate this logarithm from the biological results obtained with the lower members, a straight line drawn through these points will reach an extrapolated point at which log α approaches zero. At this juncture the member will be located which should exert the same biological activity near zero. In practice, this higher member lying along the straight line just before the "cut-off" may vary by one or two carbon atoms from the theoretically predictable member. Nevertheless, this method offers a valuable approach to estimate biological activity in a homologous series.

II. THE EFFECTS OF CERTAIN STRUCTURAL GROUPS

An insight into the effect of individual structural groups on the physiological action of organic compounds has been gained mainly by purposely altering the structure of drugs of known activity. As new groups are introduced into their molecules, or removed by chemical degradation, the resulting compounds usually exhibit gradually altered biological properties.

Another approach is to study the metabolic fate of a compound in a cell culture, a surviving tissue, or in a living animal. Certain compounds are detoxicated under these conditions, and the chemical changes leading to the less toxic (i.e., less active) derivatives permit some conclusion concerning the influence of structural factors on activity. Other chemicals though they may be devoid of activity, are converted to active compounds during their changes in the tissues, and if the metabolic products can be isolated and compared with the original drug, similar conclusions can again be drawn.

Care must be exercised in interpreting the effects of structural changes. A new chemical structure means a new set of reactions between drug and body or cell constituents, and thereby perhaps a new mechanism of action. However, alterations of the functional groups may also change primarily such physical properties as the solubility of a compound, and in this way alter its absorption and distribution characteristics on cell membranes and in tissues. The term "change of physiological action by alteration of chemical structure" thus assumes a broad meaning, incorporating both the act of the drug in reaching the place of action, and the mode of action itself after the drug has reached the proper body chemicals.

As mentioned before, no overall predictions can be made about the effect of structural variations on biological activity. It seems rather fruitless to discuss at length this problem whose success is so questionable. Fifteen years ago, no other avenue was open to medicinal research, and consequently all books and articles of that era contained long introductory chapters on this subject. No less than 118 pages are devoted to generalizations about structure-action relations in Fränkel's classical work on pharmaceutical chemistry,[5] but a careful count of the deviations from the rules shows an almost even balance of regularities and irregularities. Recognizing the relative futility of such thoughts, only a brief discussion of these relations will be offered here. They will be dealt with in detail in the individual chapters of this book, since the gradual variation of chemical structures has been the most useful and realistic approach to better drugs *in a structurally limited series*. In some cases it will be possible to point to other series of drugs in which analogous structural changes produce analogous gradations of biological response.

1. Reactivity and Intensity of Action

In many series of compounds, intensity of biological activity is proportional to chemical reactivity. The paraffins are less active as anesthetics and toxic agents than the corresponding olefins, cycloalkanes, acetylenes or aromatic hydrocarbons. Their narcotic action increases in homologous series but is limited by loss of solubility and volatility among the higher members.

(a) Alkyl Groups

Whenever an alkyl group replaces a reactive hydrogen atom ($HCN \rightarrow RCN$; $ArOH \rightarrow ArOR$; $RNH_2 \rightarrow R_2NH$), the over-all biological activity of the alkylated compound is lower than that of the non-alkylated deriva-

[5] Fränkel, *Die Arzneimittelsynthese*. 6th ed., Urban & Schwarzenberg, Berlin, 1927.

tive. This rule has, however, many exceptions. Some simple alkylamines are more toxic than ammonia, ethers more toxic than alcohols (ROH, ROR), and the dimethyl ether of resorcinol (1,3-$(CH_3O)_2C_6H_4$) is more toxic than resorcinol. But with toxicity and physiological activity not being equal, one cannot rely too heavily on this comparison.

Different alkyl groups endow a basic structural unit with different physical properties. Higher alkyl ethers have lower melting points, a higher lipid solubility and lower volatility than methyl ethers, and these properties influence medicinal qualifications in various irregular ways. There are some rather striking phenomena in this series which defy explanation. Certain dyes containing diethylamino groups dye nerve fibers while the corresponding dimethylamino compounds do not have this ability. *p*-Methoxyphenylcarbamide ($CH_3OC_6H_4NHCONH_2$) is tasteless while the ethoxy analog (Dulcin) is 200 times as sweet as sucrose. Finally, removal of the two methyl groups from the molecule of the trypanocidal drug Suramine ($C_{49}H_{40}N_6O_{23}S_6$, see Chapter XXXVII), reduces the effectiveness about one-hundred times. It is hard to see what influence two methyl groups could have on solubility, or steric configuration of such a large molecule.

If alkyl groups neighbor reactive positions, they may exert steric blocking and thereby restrict the reactivity of the compound. This lowered reactivity can, in turn, reduce the biological activity of the drug in comparison with a sterically unhindered *nor*-derivative.

(b) Amines

Primary amines are usually more toxic, and often more active, than secondary amines, and the latter are followed by tertiary amines. The highly ionized quaternary ammonium bases and their quaternary isologs, sulfonium, arsonium and phosphonium compounds act most intently and cause curariform paralysis in small dosages (Chapter XXII). Acylation of amino groups quite generally decreases their activity, as does the introduction of carboxyl or sulfo groups into their molecule, since the latter groups reduce the reactivity of the amino group by zwitterion formation. Vice-versa, diamines are more active than monoamines. Many aromatic amines with free *p*- or *o*- positions are oxidized to the corresponding aminophenols, and since the latter are readily dehydrogenated to quinoid derivatives, their physiological activity is often greater and yet more specific than that of the parent amines.

(c) Alcohols and Phenols

Alcohols are more weakly depressant than their parent hydrocarbons, and diols, triols, etc., show progressively less intense physiological activity. Propanol is much more active than glycerol, hexanol more than sorbitol; butyraldehyde is more active than its β-hydroxy derivative, aldol, and the toxic hexaldehyde can barely be compared with the medicinally inert glucose. Only if the alcohol is particularly easily metabolized to a highly toxic product (ethylene glycol to oxalic acid) will the observer get a picture of unexpected toxicity.

It is difficult to draw up a rule about the relative activity of primary, secondary and tertiary alcohols. One would expect that tertiary alcohols are so sterically hindered that their most common biological reaction, esterification, should proceed very slowly. Also, they cannot be dehydrogenated, in contrast to primary and secondary alcohols which yield aldehydes and ketones, respectively. Yet, tertiary alcohols, are the most active of the three types, perhaps because of their ability to form carbonium ions.

Etherification of hydroxyl groups generally decreases further physiological activity. So does esterification, as long as conditions are unfavorable to an easy hydrolysis of the ester which could bare the reactive hydroxyl group. It would be wrong to conclude from these facts that the hydroxyl group is responsible for a particular biological activity, but it appears that it anchors the molecule on a reactive position of a cell chemical. This view has been elaborated recently in connection with cholinergic drugs (Chapter XXI).

Phenols are acidic compounds and are, in contrast to the alcohols, much more toxic than their aromatic parent hydrocarbons. Polyphenolic compounds are even more poisonous. On the other hand, introduction of a carboxyl or sulfonic acid group modifies and decreases their biological activity. If the acid group is immobilized by esterification or amide formation, the original effect of the phenolic compound returns in considerable measure.

(d) Aldehydes and Ketones

Aldehydes are usually more reactive than ketones and consequently exhibit a more intense biological activity. Formaldehyde is a potent antiseptic, killing cells and hardening tissues by precipitation and coagulation of proteins. Ketones are pharmacologically more like the corre-

sponding secondary alcohols, but both aldehyde and keto groups occur in such a wide variety of compounds that generalizations are not possible. One may think of such divergent aldehydes as vanillin, streptomycin and chlorophyll-b to realize the difficulties of drawing any well-supported conclusions.

(e) Acids

The introduction of carboxyl, sulfonic, arsonic, phosphonic and other acid groups into the molecule of an active or poisonous drug generally sharply lowers its biological potency. Nitro, amino, and hydroxy compounds become less active or even completely inactive pharmacologically. The difference between a poisonous proteinogenous amine (RCH_2NH_2) and the corresponding amino acid ($RCH(COOH)NH_2$) is a case in point. The amino acids are largely interesting as food stuffs, while the amines produce striking medicinal effects. A similar decrease of biological properties has already been mentioned above for the covering-up of a reactive group by acyl radicals. Amides and esters are generally less active than the parent amines, alcohols or phenols.

(f) Halogens

Depending on their electrochemical nature, halogens exert a pronounced influence on the biological behavior of organic compounds. Halogen substituted in nonconjugated positions ("negative halogen") usually increases both useful and toxic properties of active compounds, but not at the same rate. The increase in toxicity is often negligible, and many medicinal chemists look upon halogen substitution as a reasonable means of stepping up activity, and widening the margin of safety in a given series.

The so-called positive halogens in acid chlorides, α-halogeno carbonyl compounds, etc., have the opposite effect. Their toxicity decreases as the number of positive halogens is augmented, and other anomalies are also noted. Compounds having "available" halogen (chloramines, Chapter XXXXIII) are strongly antiseptic, in proportion to the percentage of hypohalous acid they can furnish on hydrolysis.

There is no clear-cut difference between the activities of organically bound chlorine, bromine and iodine. More antiseptics seem to have been found among iodinated compounds, but this statement may well be disputed. Brominated derivatives have been said to lean toward depressant properties, but this generalization would again not stand up under statistical analysis. Fluorinated compounds appear to be much less physiologically active than derivatives containing other halogens, and even less

than the corresponding non-fluorinated substances. This anomalous behavior may be caused by the stability of fluorine derivatives which owe their inertness to the shortened distance between carbon and fluorine atoms, and to the strong resonating effects in their molecules. This phenomenon fits into the general picture of a parallelism between reactivity and physiological activity. It is noted in many compounds which contain reactive elements. The vesicant mustard gas [$(ClCH_2CH_2)_2S$] is detoxicated, when its reactive sulfide atom is oxidized to the inert sulfone group [$(ClCH_2CH_2)_2SO_2$].

The foregoing brief remarks must leave with the reader a feeling of dissatisfaction. It seems that it is not possible to correlate chemical structure and action upon living cells to any degree of accuracy. One obvious reason for this failure lies in the working method applied to this problem: we have contemplated what changes in biological activity will accompany given changes in chemical structure. One arrives at a more satisfactory picture if instead of these two variables, only one variable is chosen. We can pose the question: how far can we change the chemical structure of a compound without altering its physiological properties? An attempt to answer this question is made by trying to correlate the physical properties of a compound with its pharmacological activity, and this comparison may be discussed conveniently in connection with the theory of isosterism.

CHAPTER IV

Physical Properties and Biological Activity

The physical properties of a compound depend on its chemical structure, and it is therefore obvious that not much can be gained by a comparison of physical properties and biological activity, if a similar comparison with purely structural factors has remained inconclusive. However, so much work has been done on this problem that a few remarks about its outcome are in order.

The most obvious physical properties which lend themselves to investigation are acid and basic dissociation and other electrical constants, densities, surface phenomena, molecular weights and shapes, optical properties (spectral, refraction, polarization, etc.), atomic distances, parachor, specific heats and other thermal data. There is no doubt that in a given limited series of structurally related compounds, progressive changes of certain physical properties follow the same trends as the analogous changes of biological manifestations. However, here again we cannot carry over such limited regularities to other groups of compounds, and we are faced with the same restrictions imposed by our understanding of structure-and-action relationships.

In view of this lack of overall regularities, this volume will review the relations of physical and physiological properties only in the individual chapters devoted to the description of a given series of drugs. In lieu of a condensed enumeration of many unrelated observations in different series, the following section on isosterism will present a more unified view of these relations with only one variable property.

I. ISOSTERISM[1]

The concept of isosterism was evolved in an attempt to correlate the structure and properties of molecules, especially those with similar electron patterns, in analogy to the relationship of atoms with identical valence electron shells. As the study of this phenomenon progressed it was hoped that predictions could be made based on such relations, just as predictions of the properties of elements had become possible by the evolution of the periodic table. Unfortunately, complicating and poorly understood

[1] Adapted and abridged from the thesis of Dr. Edith A. Graef, University of Virginia, Charlottesville, Virginia, 1946.

effects of steric and electrical forces of the atomic constituents in more complex molecules have caused some confusion in defining isosterism. But, in the absence of any other comprehensive correlation of the properties of compounds and their molecular structure, speculation along these lines has remained attractive.

On the basis of the rather ill-defined term of isosterism, many medicinal chemists have planned research projects designed to lead to compounds of similar actions as those of model drugs. More often, isosterism has been invoked *post facto* to explain the similarity of physiological activity of structurally analogous compounds. Some investigators have stretched structural analogies beyond all physical evidence of likeness. In view of this confusion, a brief survey of isosterism as it applies to medicinal chemistry seems indicated.

Isosteric molecules must not necessarily be closely similar in all properties, but if their "electrical fields" and molecular weights were identical or almost identical, a definite resemblance of properties should exist. The concept of electrical fields is not too clearly defined but a few of the more patent factors determining this entity are suggested in the following list: (*1*) Number and type of electrons. (*2*) Charge on the isosteric molecules. (*3*) Type of binding. (*4*) Dipole Moments. (*5*) Resonance Energy. (*6*) Tautomerism. (*7*) Chelation.

One can see that compounds exhibiting similar physical phenomena as they are listed above should have not only a similar complex of electrical properties, but also a similar shape and size, provided their molecular weights are not too far apart. This similarity of properties should be reflected in a similarity of physiological activity. However, not only close analogy of biological properties but also antagonism of pharmacological behavior between isosteric compounds has been observed frequently. Compounds structurally and physically closely related to blood coagulants have been found to have anticoagulant properties. Compounds which are needed by cells as normal nutrients (metabolites) can be turned into inhibitors of cellular life (antimetabolites) by suitable, often minor structural variations. The significance of this phenomenon for drug research is obvious. We might be able to construct molecules of compounds potentially useful in combatting bacterial infections if we know the structure of bacterial metabolites. By altering the structure of hormones, we could synthesize drugs which might counteract hyperactivity of these biocatalysts in the body. So important has been the impact of this hypothesis on medicinal thinking that it will be discussed in a special chapter (XXXII) and will be found to pervade many considerations in this book. We do not yet have any rules to guide us where similarity of biological properties will end, and antagonism will begin in isosteric com-

pounds. As Pauling[2] put it, "the specificity of the physiological activity of substances is determined by the size and shape of molecules, rather than primarily by their chemical properties, and the size and shape find expression by determining the extent to which certain surface regions of the molecules can be brought into juxtaposition."

1. Theories of Isosterism

(a) Early Explanations

The basic ideas underlying all the theories of isosterism were developed in inorganic chemistry in order to show that a structural analogy must exist between nonisomeric molecules showing a marked similarity in physical, chemical and physiological properties. In what seems to have been the first attempt to explain such similarities, Moir[3] in 1909 suggested that atomic nitrogen would be found not to be an element, but a compound CX, where X was an unknown element of atomic weight 2, and that oxygen was a similar compound CX_2. This prediction was based upon the known physical similarities of carbon monoxide and nitrogen which, according to Moir's ideas, would be isomeric, both being C_2X_2. Seven years later Hinsberg[4] tried to deduce the shape of molecules by the same mode of reasoning. Because of the striking resemblance of benzene to thiophene and pyridine, he thought that divalent sulfur and the group —CH=CH— must be "ring equivalents," as must —N= and —CH=. Sulfur, therefore, should resemble —CH=CH— in its external form; in a model of this similarity, no attention was paid to the two hydrogen atoms of the —C_2H_2— group, since "they would be swallowed up by the much larger carbon atoms." This concept has remained a favorite practice of later workers.

Allen[5] approached the problem from a different angle. He defined the molecular number of a compound —A_aB_b— as $N = aN_A + bN_B + \cdots$ where N_A, N_B, etc. are the corresponding atomic numbers. In the case of ammonium ions, NH_4^+, the molecular number, 11, equals the atomic number of the similar sodium ion. He further found simple relationships between the product of a characteristic frequency and the molecular number and the specific heat or other physical properties.

This molecular number of Allen's is obviously the total number of electrons in the molecule, and hence those compounds which Allen found

[2] Pauling, *Chem. Eng. News*, **24,** 1375 (1946). Compare Breinl and Haurowitz, *Z. physiol. Chem.*, **192,** 45 (1930); Mudd, *J. Immunol.*, **23,** 423 (1932); Alexander, *Protoplasma*, **14,** 296 (1931); Pauling, *J. Am. Chem. Soc.*, **62,** 2643 (1940).

[3] Moir, *J. Chem. Min. Soc. S. A.*, **98,** 335 (1909); *Chem. News*, **124,** 105, 118, 133 (1922).

[4] Hinsberg, *J. prakt. Chem.*, **93,** 302 (1916); **94,** 179 (1916).

[5] Allen, *J. Chem. Soc.*, **113,** 389 (1918); *Phil. Mag.*, **35,** 338 (1918).

similar on the basis of molecular number are exactly those which fulfill the conditions Langmuir[6] set up for isosteric molecules. In his papers on the development of the octet theory, he mentioned that, in order to have such a low boiling point, nitrogen must have a symmetrical molecule, and that carbon monoxide must have a similar structure. Nitrogen and carbon monoxide are isosteric, because they have the same number and arrangement of electrons. This definition can be extended to any other pair of isosteric compounds. Furthermore, if they are also isoelectric, that is, have the same total charge on the comolecules, the compounds may be expected to show close similarity in all their physical properties. Langmuir cited not only the case of nitrogen and carbon monoxide but also those of carbon dioxide and nitrous oxide, methane and argon, etc. In the organic field, he predicted the similarity of diazomethane (CH_2N_2) and ketene ($CH_2{=}CO$), the latter being then unknown. This prediction has been borne out by later observations.[7]

(b) The Hydride Displacement Law

Soon thereafter Hückel[8] pointed out that —CH= should be equivalent to —N= in organic compounds, and —NH— the equivalent of —O—. This concept was elaborated by Grimm into the "hydride displacement law" formulated in Table I.

TABLE I. Grimm's Hydride Displacement Law[8]

Number of electrons				
6	7	8	9	10
C	N CH	O NH CH_2	F OH NH_2 CH_3	Ne FH OH_2 NH_3

Grimm believed that molecules differing only by such replacements as, for example, ethyl fluoride, ethyl alcohol, ethylamine and propane (*vide*, the 9-electron vertical column), may appear chemically wholly different and yet be analogous in physical properties. He used the term pseudoatom for groups such as —OH or —NH_2, and said that one could predict from analogies based on his table definite physical values dependent on molecular size and electron configuration, on condition that these properties be relatively unaffected by dipole moments.

[6] Langmuir, *J. Am. Chem. Soc.*, **41,** 868, 1543 (1919).
[7] Murty, *Current Sci.*, **5,** 424 (1937); *Chem. Abstr.*, **31,** 4644 (1936).
[8] Hückel, *Z. Elektrochem.*, **27,** 305 (1921). Grimm, *Angew. Chem.*, **42,** 367 (1929); **47,** 53, 594 (1934); *Z. Elektrochem.*, **34,** 430 (1928); *Naturwiss.*, **17,** 535, 557 (1929).

In the formulation of this idea, Grimm thought that in each pseudo-atom such as the imino group, the hydrogen proton is absorbed within the inner electron orbits of the nitrogen atom, and the hydrogen electron goes over into the general "molecular orbits," the resultant effect being that of an atom of $z + 1$ charge. Such a condition is allowed[9] if one atom is small enough, a proviso satisfied by hydrogen if by anything. In atoms larger than nitrogen the hydrogen, according to this theory, will be absorbed only within the outer valence electron orbits. The inner atomic orbits in every case must remain unchanged as shown by X-ray spectra of molecules. This concept of Langmuir's picture has been applied to show that the pseudo-halogen molecules, HO—OH, NH_2—NH_2, and CH_3—CH_3, all have the same number of electrons and the same type of binding.[10] Any pseudo-halogen obeys the relationship:

$$\Sigma(\text{outer electrons}) + \Sigma(\text{binding electrons}) = 8n + 2m - 1$$

where n is the number of atoms surrounded by an electron orbit, and m is the number of hydrogen atoms of the radical. Thus, for the cyanide radical, ·C:::N:, the number of outer electrons is nine, the number of binding electrons is six, $n = 2$, and $m = 0$; then $9 + 6 = 15 = 8 \times 2 - 1$.

In an elaboration of Grimm's hypothesis, Erlenmeyer[11] postulated that, if only the outer electrons in a molecular orbit arising from the entire molecule are considered, one can never arrive at an identity of properties but only at a constant variation between groups.

This concept of molecular orbits was applied to formulate a system of inorganic acids and retained the static idea that although electrons move they nevertheless remain in fixed orbits. This was later contested not only on the basis of the quantum theory with its insistence on probable electron density rather than mechanical orbits, but also more drastically, on the basis of electron resonance. One must consider, therefore, more factors than the total number of electrons in deciding whether two compounds are isosteric or not; that is, the term must be redefined. These other properties include similarities in melting points (if possible, formation of mixed crystals), boiling points, densities in the liquid state, critical temperatures, pressures and volumes, and molecular weights.

(c) Steric Factors

The idea that isosteric molecules must possess equal form and volumes has been firmly accepted by many investigators. Physical evidence for

[9] Mulliken, *Chem. Revs.*, **9,** 347 (1931).
[10] Hückel, *Z. Elektrochem.*, **27,** 305 (1921).
[11] Erlenmeyer and Leo, *Helv. Chim. Acta*, **16,** 897 (1933). Erlenmeyer, *Z. physik. Chem.*, B, **27,** 404 (1934).

and against this assumption has been presented on numerous occasions. On the basis of *Cp/Cv* values, viscosity measurements, and the fact that aberrations of specific heat values may be due to "internal vibrational and rotational energies," diphenylmethane and diphenyl ether were shown to have approximately the same collision areas.[12] Pease used the van der Waal's *b* values for comparison; in his experiments, he did not assume that the hydrogens of pseudo-atoms were swallowed up but rather sought to prove that the groups minus hydrogen were identical in volume. Many other methods of volume and shape comparison have been used, based on the similar mobilities of isosteric ions,[13] densities of complex ions,[14] atomic and ionic radii,[15] and additive functions such as the parachor of isosteric molecules.[16] One can even derive a rule showing that the shape of molecules is bound up with the valence electron pattern.[17]

The conclusion that isosteric molecules must have equal volumes and similar shapes has led many students of isosterism to believe that such compounds must form mixed crystals, and the majority have used melting points and melting point curves as the single criterion of isosterism. General statements have been made that methyl replaces chlorine and bromine but not iodine isomorphically in organic compounds, or that hydroxyl and fluorine are isomorphic. Ultimately, two hundred pairs of isosteric compounds were studies for mixed crystal formation, but only forty-nine showed mixed crystals over the whole range of percentage composition, and to this low percentage can be added only another thirty-four pairs which showed mixed crystals over part of the composition range.

The net result of these studies[18] is that isosteric compounds are isomorphic in the Langmuir sense, but that mixed crystal formation may or may not occur, the reason for its occurrence being at present unknown. Maybe not only the size of the crystal unit but also the polarization must be identical. Some authors have stated that the solubility as well as the crystal form must be similar for mixed crystal formation to occur. This condition is not generally satisfied by isosteric molecules, principally because of the influence of the dielectric constants on solubility. While this is negligible for solvated isosteric ionic salts which form mixed crystals, it assumes great importance for isosteric molecules.

[12] Hare and Mack, *J. Am. Chem. Soc.*, **54,** 4272 (1932). Rankine, *Nature*, **107,** 203 (1921). Menzies, *ibid.*, **107,** 331 (1921).
[13] Birckenbach and Huttner, *Z. anorg. u. allgem. Chem.*, **190,** 38 (1930).
[14] Hieber, Ries and Bader, *ibid.*, **190,** 215 (1930).
[15] Goldschmidt, *Ber.*, **60,** 1263 (1927).
[16] Copley, *Chemistry & Industry*, **59,** 675 (1940).
[17] Zachariasen, *J. Am. Chem. Soc.*, **53,** 2123 (1931).
[18] Erlenmeyer and Berger, *Biochem. Z.*, **255,** 429 (1932). Erlenmeyer and Leo, *Helv. Chim. Acta*, **16,** 897 (1933). Erlenmeyer, *Z. physik. Chem.*, B, **27,** 404 (1934). Grimm, Günther, and Tittus, *ibid.*, **14,** 169 (1931).

2. Other Physical Properties

With isomorphism placed in such an uncertain position as a criterion of isosterism, other physical properties have been compared for this purpose. The boiling points of analogous benzene and thiophene derivatives show a striking similarity, but unfortunately not in all cases.[19] For simpler compounds such as dimethyl ether, dimethylamine, propane, etc.,[20] as well as for methyl fluoride, methanol, methylamine and ethane,[21] no definite regularity can be observed. Likewise, comparisons of ionization potentials[22] and the decomposition voltage of pseudohalogens do not indicate valuable points of comparison. The acid dissociation constants of isosteric heterocyclic acids show additive differences,[23] and the dipole moment factor again appears to explain some of these differences. While reduction-oxidation potentials do not depend closely on dipole moment, the acid potential does, the dissociation being the greater the more electron-attracting the substituent groups are. An important case of this regularity is the acid dissociation of sulfa drugs where the extent of ionization depends upon the electro-negativity of the substituent R in p-$H_2NC_6H_4SO_2NHR$.[24] Closely related to the evaluation of dissociation potentials is the measurement of absorption wave lengths. Studies along these lines have furnished variable results. If, for example, the intensity of absorption as log E is plotted against the wave length for a series of isosteric compounds, the curves are by no means coincidental or even geometrically similar, but are nevertheless of the same type, and the maxima and minima occur at the same wave lengths.[25] If the compounds contain asymmetric carbon atoms bonded to isosteric groups, their optical activity is also very similar. This was observed for benzoin and its chloro and methyl analogs,[25] as well as for cocaine and its thiophene isostere[26] (Chapter VIII).

Comparisons of the conductivity of isosteric compounds have shown that, for pseudohalogens, it differs because of unequal degrees of hydration and not because of another innate disparity.[27]

[19] Steinkopf and Lützkendorf, *Ann.*, **403,** 45 (1914). Robinson and Todd, *J. Chem. Soc.*, *1939*, 1743.

[20] Grimm, *Z. Elektrochem.*, **31,** 474 (1933).

[21] Schnieder, *ibid.*, **36,** 700 (1930).

[22] Birckenbach and Kellermann, *Z. anorg. u. allgem. Chem.*, **190,** 1 (1930). *Naturwiss.*, **18,** 530 (1930).

[23] Erlenmeyer, Epprecht, and Meyenburg, *Helv. Chim. Acta*, **20,** 310 (1937).

[24] Bell and Roblin, *J. Am. Chem. Soc.*, **64,** 2905 (1942); compare Chapter XXXIV.

[25] Preiswerk and Erlenmeyer, *Helv. Chim. Acta*, **17,** 329 (1934).

[26] Steinkopf and Ohse, *Ann.*, **437,** 14 (1924).

[27] Birkenbach and Huttner, *Z. anorg. u. allgem. Chem.*, **190,** 38 (1930).

3. Effects of Isosteres on Reactivity

The catalytic effect on a standard reaction such as the Menschutkin reaction ($EtI + Et_3N \rightarrow Et_4NI$) of a series of solvents differing by the hydride displacement law does not wholly parallel the dielectric constants of the solvents, but rather parallels the melting and boiling points. In these properties, the asymmetric form of a single part of the molecule of the isostere must be decisive.[28] If benzene, thiophene and furan are used as reaction solvents, no relation exists between the reaction velocity and the dielectric constant or the viscosity.[29] Since the dielectric constant is not the only criterion of a good solvent for ions, such relations would not necessarily be expected.

Aside from such collations of physical properties, many comparisons of the chemical reactivity of isosteres have also been made. More important for the scope of this volume is a comparison of biological activities.

4. Classification of Isosteres

One criterion of a similar electrical field in physiologically similar isosteres is the requirement that the number of electrons be approximately the same and, more important, that the resultant angular momentum be the same. For example, in thiophene and benzene the total number of electrons differ by 2, but their angular momentum can be shown to be the same. One might conveniently define isosteric compounds of the first order as two compounds which differ only by two groups containing the same number and kind of electrons, e.g., —CH: and —N: each of which has seven electrons, two of major quantum number 1, and five of major quantum number 2. Such compounds cannot be expected *a priori* to show similar physical properties, except that they will have equal volumes and similar shapes unless greatly deformed by a strong electrical field. That is, the volume will be more nearly identical if the molecules are highly dispersed and not under electrical influences.

Isosteric compounds of the second order may differ in the total number of electrons, but have the same resultant electronic state; i.e., they may have roughly the same number (p) of unpaired electrons of the same major quantum number, or $n-p$ unpaired electrons where n is the total number of electrons allowed with the given major quantum number. This latter case is not often considered in practice. Such isosteres will again not necessarily have similar physical properties—as demonstrated in the earlier part of this chapter—but if their total number of electrons

[28] Grimm, Ruf, and Wolff, *Z. physik. Chem.*, **13,** 301 (1931).
[29] Erlenmeyer and Leo, *Helv. Chim. Acta*, **16,** 1381 (1933). Meerwein and Emster, *Ber.*, **55,** 2500 (1922).

is not too widely different, they will probably have similar volumes and shapes. Copley's parachors are recommended as a convenient test. This *similarity in size and shape* thus becomes the paramount prerequisite for analogous or antagonistic physiological activity.

A further important property which must be considered in defining isosterism in physiologically similar compounds is the dipole moment, the measurement of the relative displacement of centers of opposite charge. If a large dipole exists, the electric field is obviously distorted, and this will affect physical and chemical properties, particularly those which depend on the asymmetry of the molecules, and on molecular association resulting from dipole attractions. The solubility, boiling point, heat of vaporization, change of vapor pressure with temperature, and change of viscosity and surface tension with temperature may all be expected to differ for two isosteric compounds having different dipole moments. To this must be added the resonance possibilities of isosteric molecules, since resonance changes the basic ground level energy of a molecule and hence its stability. The resonance energies of a few selected isosteres have been measured and have been found to agree with the predicted properties of isosteres, but the agreement was probably closer and more generally apparent than would have been the case in a more comprehensive survey.

Inasmuch as resonance stabilizes each tautomeric form, it exerts indirectly an effect on its chemical reactivity, spectra, solubilities, etc. Chelation must also be considered in comparing isosteres, since this property affects boiling points, solubilities, and other physical properties.

Complications arise usually from the interaction of these factors among themselves and with others such as steric hindrance. It is fortunate for the practical medicinal chemist that so often isosteres seem to show somewhat the same physiological action without regard to these other considerations. But for the scientifically correct evaluation of isosterism, it is obviously not sufficient to determine one or two physical properties, and to call compounds isosteric if they happen to conform to the rule rather than to the exception in these respects. Only by measuring *all* the properties affected by electronic configuration as well as dipole moments can we arrive at a sound interpretation of this fascinating phenomenon.

5. Biological Activity of Isosteres

The idea that a given type of biological activity is due to the energy field at one active part of the molecule, the "haptophore" or "pharmacophore" group, has been reiterated time and again during the past seventy years, ever since Ehrlich introduced these terms in his early studies of immunological reactions. It has received renewed attention very recently in the discussion of Ing, and of Pfeiffer (Chapter XXI) concerning the chemical cause of cholinergic activity.

Biological activity is similar, or occasionally diametrically opposed (antagonistic) in isosteric compounds. Isosteres cannot be distinguished by serological reactions since many of them produce antibodies which give the same strong reactions with homologous antigens. Thus, *p*-aminodiphenylamine, *p*-aminodiphenylmethane, and *p*-aminodiphenyl ether all show the same antigen activity.[30]

In an earlier attempt to prove that only the outer electronic shell had to be the same in isosteres, it was found that, for compounds of the type *p*-$H_2NC_6H_4MO_3H_2$, where M is phosphorus or arsenic, the antigenic activity is the same; whereas if M is antimony, the activity is wholly different. This appears to agree with the known isomorphism of phosphoric and arsenic acids while antimonic acid seems to exist only in a polymeric form.

Tables II, III and IV review the physiological comparison of some isosteres. The compounds have been arranged according to isosteric groups (N:CH, O:NH, O:CH_2, etc.). Many of these comparisons will be re-encountered in other chapters of this book, where structural formulas will also generally be found.

One cannot draw a dogmatic conclusion from the observations recorded in these Tables that any or all properties of isosteric molecules must be closely similar. Yet, the comparisons support the belief that definite physiological resemblance or antagonism involve identical, or almost identical, electrical fields, molecular weights and molecular shapes.

TABLE II. PHYSIOLOGICAL ACTIVITY OF ISOSTERIC COMPOUNDS WITH SAME TOTAL NUMBER OF ELECTRONS, AND HAVING SAME VALENCE SHELLS

Isostere (a)	Isostere (b)	Physiological action
	N...CH	
Diphenylamine	Diphenylmethane	Same antigen activity[31]
Dimethylaminoantipyrine	Isopropylantipyrine	Great similarity in action and toxicity[32]
Benzimidazole	Adenine	Antagonists[33]
2-Amino-5-carboxypyridine	*p*-Aminobenzoic acid	Similar antagonism to sulfonamides[34]
5-Amino-7-hydroxy-1-v-triazole(d) pyrimidine	Guanine	Antagonists[35]
	O...NH	
Diphenyl ether	Diphenylamine	Same antigen activity[31]
Oxythiamine	Thiamine	Antagonists[36]
Dicumarol	Quinolone analog	(a) is hemorrhagic (b) 1/50 as active[37]

Table continued

[30] Erlenmeyer and Berger, *Biochem. Z.*, **255,** 429 (1922); **264,** 113 (1931).

TABLE II. (*Continued*)

Isostere (a)	Isostere (b)	Physiological action
	O...CH_2	
Diphenyl ether	Diphenylmethane	Same antigen activity[31]
Nicotinic Acid	3-Acetylpyridine	Antagonists[38]
Isobarbituric Acid	Thymine	Antagonists[39]
	NH...CH=CH	
Indole-3-acetic Acid	1-Naphthylacetic Acid	Similar heteroauxin activity
Indole-3-acrylic Acid	1-Naphthylacrylic Acid	Similar, tryptophan antagonists[40]
5-Methylacridine Amino alcohols	Phenanthrene Amino alcohols	Analgetics[41]
	O...CH=CH	
2-Furylethylamine	Phenethylamine	Same effect on blood pressure[42]
2-Furylmethylamine	N-Methylaniline	Same effect on blood pressure[42]
2-Methylamino-3-furylpropanol	2-Methylamino-3-phenylpropanol	Same effect on blood pressure[42]
2-(2-Furyl)-4-carboxyquinoline	Cinchophen	Both analgetic and anti-pyretic[42]
Furan isolog of cocaine	Cocaine	Similar[42]
Furan isolog of procaine	Procaine	Similar[43]
Dibenzofuran	Phenanthrene	Similar, graded activity[44]
	S...—CH_2CH_2—	
Biotin	Cyclohexane analog of biotin	Antagonists[45]

[31] Erlenmeyer and Leo, *Helv. Chim. Acta*, **26,** 733 (1943). Erlenmeyer, *Biochem. Z.*, **252,** 22 (1932); **262,** 196 (1933).
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[33] Woolley, *J. Biol. Chem.*, **154,** 31 (1944).
[34] Martin, Rose, and Swain, *Nature*, **154,** 639 (1944).
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[36] Bergel and Todd, *J. Chem. Soc.*, 1504 (1937). Soodak and Cerecedo, *J. Am. Chem. Soc.*, **66,** 1988 (1944).
[37] Link, *Harvey Lectures*, 1944. Meunier, Mentzer, Buu-Hoi, and Cagniant, *Bull. soc. chim. biol.*, **25,** 384 (1943).
[38] Woolley, *J. Biol. Chem.*, **157,** 455 (1945).
[39] Hitchings, Falco, and Sherwood, *Science*, **102,** 251 (1945).
[40] Bloch and Erlenmeyer, *Helv. Chim. Acta*, **25,** 694, 1062 (1942).
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[42] Erlenmeyer and Simon, *Helv. Chim. Acta*, **24,** 1210 (1941).
[43] Gilman and Pickens, *J. Am. Chem. Soc.*, **47,** 245 (1925).
[44] Mosettig and Robinson, *ibid.*, **57,** 2186 (1935).
[45] English, Clapp, Cole, Halverstadt, Lampen, and Roblin, *ibid.*, **67,** 295 (1945).

TABLE III. PHYSIOLOGICAL ACTIVITY OF ISOSTERIC COMPOUNDS DIFFERING IN TOTAL NUMBER OF ELECTRONS, BUT HAVING SAME VALENCE SHELLS

Isostere (a)	Isostere (b)	Physiological action
	CH_3,OH...Br,Cl	
Isobarbituric Acid	5-Bromouracil	Both similar, thymine antagonists[39]
Riboflavin	Chloroflavin	Antagonists[46]
Thymine	5-Bromouracil	Antagonists[39]
	S...—CH=CH—	
2-(2-Thienyl)-4-carboxyquinoline	Cinchophen	Similar, analgetic and antipyretic[47]
Thiophene isolog of Cocaine	Cocaine	Similar, local anesthetic[26]
Thiophene isolog of Atropine	Atropine	Similar[48]
Thiophene isolog of Eucaine A	Eucaine A	Similar[49]
p-Amino-(2-thiophene)-anilide	*p*-Aminobenzanilide	Similar[31]
2-Carboxythiophene	Benzoic Acid	Same[50]
Thiophene isolog of Stovaine	Stovaine	Similar[49]
Thiophene isolog of phenacetin	Phenacetin	Similar[49]
Thenoyl quinine	Benzoyl quinine	Similar[49]
Thenoyl glycine	Hippuric Acid	Similar[51]
Thiophene isolog of Procaine	Procaine	Similar[43]
2-Thienylalanine	Phenylalanine	Antagonists[52]
N-Ethylthienylamine	N-Ethylaniline	Same action[53]
Dibenzothiophene amino alcohols	Phenanthrene Analogs	Similar, weaker[54]
5-Methyl-4,7-benzothienylquinone	2-Methyl-1,4-Naphthoquinone	Similar, anti-hemorrhagic[2]
Thiazole-4-carboxamide	Nicotinamide	Same action on bacterial growth[55]
Thiazole-4-carboxylic acid	α-Picolinic Acid	(a) 0.1% as active as (b)[56]
Thiazole-4,5-bis(diethylcarboxamide)	Quinolinic Acid bis-diethylamide	Both analeptic[57]
Thiazole-4-diethylcarboxamide	Coramin	Both analeptic[57]
Thiazole-5-carboxamide	Pyridine-3-sulfonic-acid	Both niacin antagonists[55, 58]
2,4-Dioxo-5,5-diethylthiazolidine	Diethylbarbituric Acid	Markedly similar (hypnotic)[59]
2,4-Dioxo-5,5-di-*n*-propylthiazolidine	Di-*n*-propylbarbituric	Markedly similar (hypnotic)[59]

Table continued

TABLE III (*Continued*)

Isostere (a)	Isostere (b)	Physiological action
2,4-Dioxo-5,5-diallyl thiazolidine	Diallylbarbituric Acid	Markedly similar (hypnotic)[59]
2,4-Dioxo-5-ethyl-5-phenylthiazolidine	Phenobarbital	Markedly similar (hypnotic)[59]
Sulfathiazole	Sulfapyridine Sulfadiazine Sulfapyrazine	Qualitatively similar bacteriostasis[56]
Thiamine	Neopyrithiamine	Antagonists[56, 59, 60]
Thiamine	Isopyrithiamine	Alike *in vitro*; unlike *in vivo*[61]
2-Aminothiazole-5-carboxylic Acid	6-Aminonicotinic Acid	(a) inactive (b) like sulfapyridine[62]

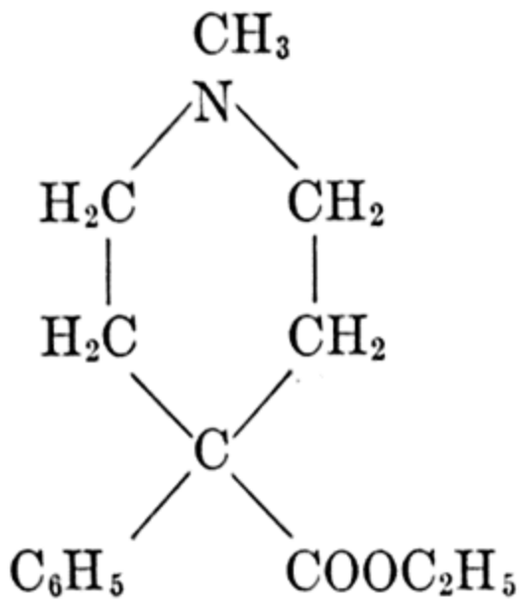
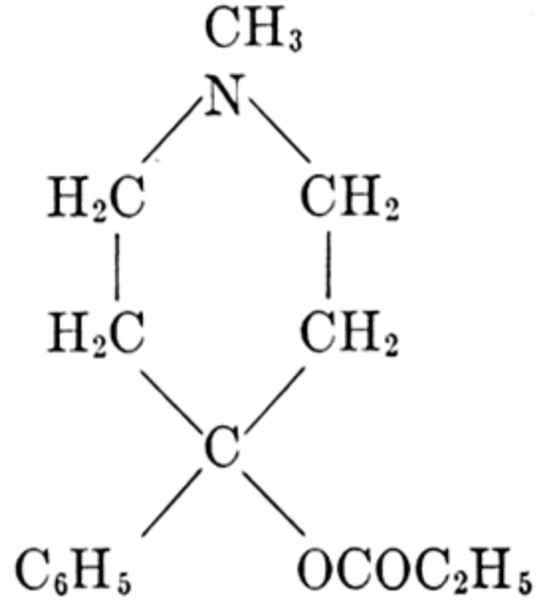
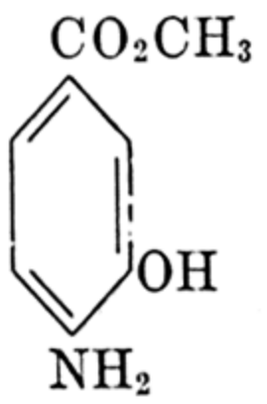
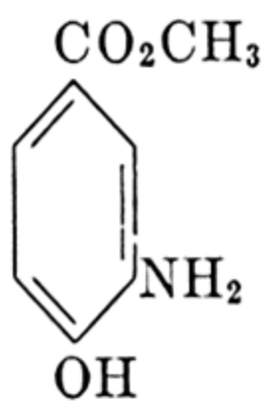
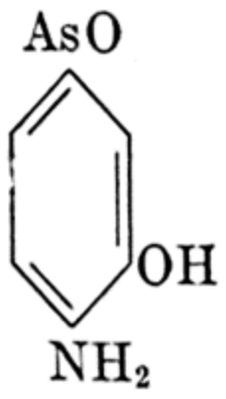
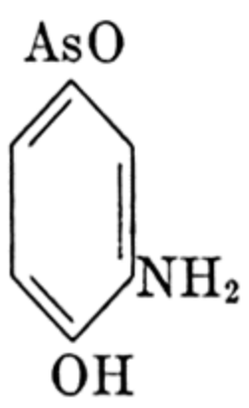
TABLE IV. PHYSIOLOGICAL ACTIVITY OF ISOSTERIC COMPOUNDS DIFFERING BY ELEMENTS IN THE SAME COLUMN OF THE PERIODIC TABLE, I.E., WITH SAME NUMBER OF VALENCE ELECTRONS, BUT DIFFERENT ELECTRON SHELLS

Isostere (a)	Isostere (b)	Physiological action
S...O		
Biotin	Oxybiotin	Same[63]
Thiouracil	Uracil	Antagonists[64]
2-Oxo-4-thiopyramidon	2,4-Dioxopyramidon	Both barbituric acid antagonists and growth inhibitors[65]
Thiodicumarol	Dicumarol	(a) has 0.1 hemorrhagic activity of (b)[37]
2-(2-Thienyl)-4-carboxyquinoline	2-(2-Furyl)-4-carboxyquinoline	Similar, analgetic[66]
Thiobarbiturates	Barbiturates	Similar[67]
2-Diethylaminomethyl-1,4-benzothioxane	2-Diethylaminomethyl-1,4-benzodioxane	Similar, sedative[68]
P...As		
Phosphonic Acids	Arsonic Acids	Same antigenic activity[31]
S...Se		
Sulfonic Acids	Selenic Acids	Same antigenic activity[31]

Friedman[69] has recently coined the term "bio-isosteric" for compounds which fit the broadest definition for isosteres and have the same type of biological activity. In several interesting tables, arranged essentially as those in this chapter, he has presented additional cases of isosterism including some instances of reversing adjacent polar groups. Examples of these comparisons are represented in Table V on page 50.

[46] Kuhn, Weygand, and Möller, *Ber.*, **76,** 1044 (1943).
[47] Hartmann and Wybert, *Helv. Chim. Acta*, **2,** 60 (1919).
[48] Steinkopf and Wolfram, *Ann.*, **437,** 22 (1924).
[49] Steinkopf and Ohse, *Ann.*, **448,** 205 (1926).
[50] Erlenmeyer, Ueberwasser, and Weber, *Helv. Chim. Acta*, **11,** 709 (1938).
[51] Jaffe and Levy, *Ber.*, **21,** 3458 (1888).
[52] duVigneaud, McKennis, Simmonds, Dittmer, and Brown, *J. Biol. Chem.*, **159,** 385 (1945).
[53] Barger, *J. Chem. Soc.*, 2100 (1938).
[54] Burger and Bryant, *J. Am. Chem. Soc.*, **63,** 1054 (1941).
[55] Erlenmeyer and Würgler, *Helv. Chim. Acta*, **25,** 249 (1942).
[56] Tracy and Elderfield, *J. Org. Chem.*, **6,** 54 (1940).
[57] Erlenmeyer and Meyenburg, *Helv. Chim. Acta*, **20,** 204 (1937).
[58] McIlwain, *Brit. J. Exptl. Path.*, **21,** 136 (1940).
[59] Erlenmeyer and Meyenburg, *Helv. Chim. Acta*, **20,** 1389 (1937). Eberly and Dains, *J. Am. Chem. Soc.*, **58,** 2546 (1936).
[60] Woolley and White, *J. Biol. Chem.*, **149,** 285 (1943). *J. Exptl. Med.*, **78,** 489 (1943).
[61] Schmelkes and Joiner, *J. Am. Chem. Soc.*, **61,** 2562 (1939). Baumgarten and Dornow, *Ber.*, **73,** 353 (1940).
[62] Johnson, Green, and Pauli, *J. Biol. Chem.*, **153,** 37 (1944).
[63] Duschinsky, Dolan, Flower, and Rubin, *Arch. Biochem.*, **6,** 480 (1945). Pilgrim, Axelrod, Winnick, and Hofmann, *Science*, **102,** 35 (1945).
[64] Roepke and Jones, quoted by Roblin, *Chem. Revs.*, **38,** 255 (1946), ref. 347.
[65] Woods, *Biochem. J.*, **36,** 4 (1942).
[66] Cuisa and Bellino, *Gazz. chim. ital.*, **66,** 452 (1936). *Chem. Abstr.*, **31,** 3487 (1936).
[67] Shonle and Doran, U. S. Pat. 2,293,770 (1943).
[68] Bovet and Benoit, *Bull. sci. pharmacol.*, **45,** 97 (1938).
[69] Friedman, "Influence of Isosteric Replacement upon Biological Activity," Symposium on Chemical-Biological Correlation, Natl. Research Council, Washington, D. C., May 26–27, 1950.
[70] Foster and Carman, *J. Pharmacol. Exptl. Therap.*, **91,** 195 (1947).
[71] Craig, *Chem. Revs.*, **42,** 285 (1948).
[72] Alles and Redeman, *J. Pharmacol. Exptl. Therap.*, **96,** 338 (1949).
[73] Eagle, Hogan, Doak, and Steinman, *Ibid.*, **74,** 210 (1942).
[74] Hartung, *J. Ind. Eng. Chem.*, **37,** 126 (1945). Kovacs and Horvath, *J. Org. Chem.*, **14,** 306 (1949).

TABLE V.[69] PHYSIOLOGICAL ACTION OF ISOSTERIC COMPOUNDS DIFFERING BY REVERSAL OF ADJACENT POLAR GROUPS

Isostere (a)	Isostere (b)	Physiological action
		(a) Demerol, analgetic (b)[70] 30 times Demerol
$(CH_3)_3N^+CH_2CO_2CH_3$ Betaine ester	$(CH_3)_3N^+CH_2OCOCH_3$ Acetyl formocholine	(a) and (b) about equally cholinergic[71]
$(C_6H_5)_2CHCOOCH_2CH_2N(CH_3)_2$	$(C_6H_5)_2CHOCO(CH_2)_2N(CH_3)_2$	(a) and (b) about equally weakly antispasmodic[72]
		(a) Orthoform (b) Orthoform New; about equally active as local anesthetics
		Virtually equally active vs. *T. Pallidum in vitro*
$3,4\text{-}(HO)_2C_6H_3CHOHCH(CH_3)NH_2$	$3,4\text{-}(HO)_2C_6H_4CHNH_2CH(CH_3)OH$	(a) Pressor (b) Inactive

CHAPTER V

Biological Study of Drugs

I. DRUGS AS ENZYME INHIBITORS

As medicinal chemicals pass through the organism and there exert their action, they affect reactions of body chemicals in a variety of ways. Apart from causing physical alterations of the osmotic pressure, membrane permeability, colloidal disperson, etc., of body chemicals, most drugs react with compounds involved in the structure or the metabolism of tissues. Likewise, drugs affecting infectious parasitic invaders react with chemicals in their cells.

The majority of drugs are administered in minute doses as compared with the weight of the treated animal or man, and yet they produce far-reaching physiological effects. The conclusion is inevitable that drugs act as catalysts, or as inhibitors of catalysts. The catalysts of metabolic processes are the enzymes, which constitute proteins with biocatalytic activity. It is now generally accepted that drugs are enzyme inhibitors. This idea has unified our concept of drug action, but it has also shown us what multiplicity of detail will have to be differentiated from case to case. The common denominator of all drugs can be expressed in one sentence: by reacting with the substrate and thereby rendering it incapable of further reactions, or by displacing substrates and serving as faulty, unaccustomed substrates, all drugs interfere with the proper functioning of enzyme systems vital for the various processes of cellular life. They produce thereby abnormal reactions resulting from unaccustomed side-paths of the altered enzymatic processes. These abnormal reactions are expressed as toxicity, unwanted in man and animals, but wanted and valuable if the cells of a pathogenic parasite are to be damaged.

Since virtually all enzymatically catalyzed reactions are reversible, drugs can straighten out faulty enzymatic processes in functional diseases of the organism. Here, aberrations are caused by hormonal, nutritive or traumatic derangements, and either speed up normal processes to a point where the equilibrium of the whole body is disturbed, or slow down vital reactions by producing faulty substrates within the body until the balance of all processes is again upset. In the former case, drugs may take over the functions of the excess substrate, and by preoccupying the overactive enzyme, permit the organism to slow down to normal. If an enzymatically

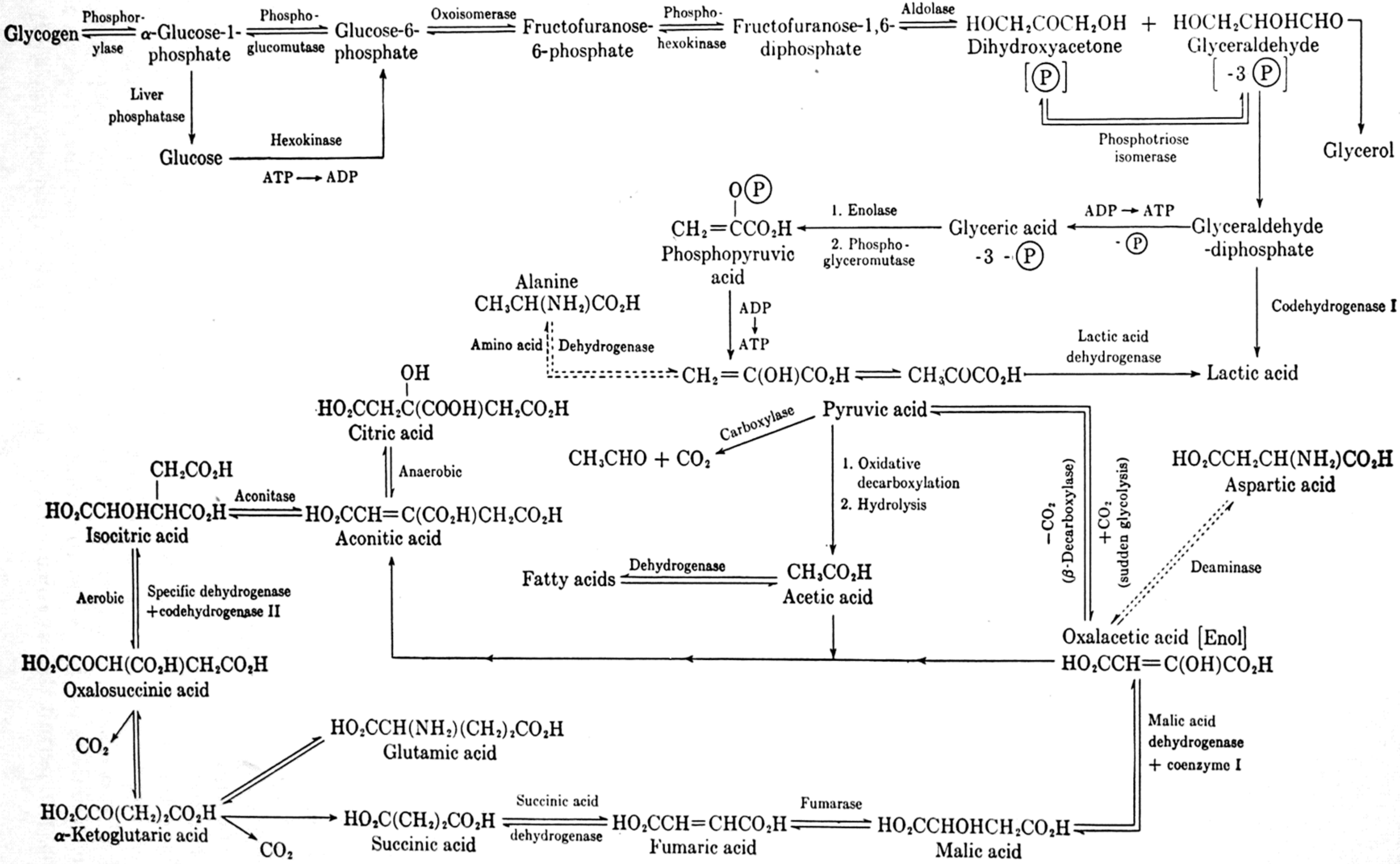


Figure 1. Schematic Sequence of the Metabolic Reactions of Glucose

catalyzed reaction has been retarded too much and symptoms of disease become apparent, a drug may either speed up the incapacitated rate of reaction, or it may activate catalytically the substrate or even alternate enzymes until a normal balance of conditions has been restored.

The realization of the multiplicity of drug action is caused by the growing understanding of enzymes, coenzymes and other essential bio-catalysts. As biochemists learn to refine their chemical and physical methods of separation, few known enzymes—even though they may have been recrystallized and purified further—have stood a rigid examination of their homogeneity. Moreover, new enzyme factors are being isolated almost daily from tissues and cells, and many of them can be integrated into known series of catalyzed reactions to aid in the understanding of the details of these cycles. It may be well to illustrate, at this point, the fallacy of attempting to interpret the action of all drugs by one scheme.

A very large proportion of all metabolic reactions—of single cells or of complex tissues depends on oxidations, reductions, hydrolyses and hydrations. The nutrients without which no cell can live are metabolized in these reactions to furnish new chemicals for cell nucleus, cytoplasm and cell wall, as well as energy for other reactions of cell constituents. Many important metabolic changes are catalyzed by dehydrogenases, and many pathological changes result from faulty dehydrogenations. A variety of drugs has been shown to react with dehydrogenases and thereby to improve, in the long run, clinical symptoms of disease. The significance of this phenomenon may be appreciated if one realizes that the most vital steps in the degradation and utilization of carbohydrates, amino acids and fatty acids are catalyzed by dehydrogenases.

A drug which inhibits many dehydrogenases plays havoc with normal health: it will prevent hundreds of dehydrogenations of different substrates, and would be a thorough systemic poison. On the other hand, a drug which inhibits selectively only *one* dehydrogenase could, conceivably, become a valuable therapeutic agent because only a single unwanted metabolic step would be blocked by its effect. There exist quite a number of compounds which inhibit just one such catalyst, but very few of them have become useful in medical practice. The reason for this unexpected failure is the integration of dehydrogenases in various metabolic cycles. In carbohydrate utilization which furnishes numerous essential metabolic intermediates and funnels energy into many activities of every tissue, the intricate processes of glycolysis and the degradation of glucose by the metabolic machine of the tricarboxylic acid cycle[1] are catalyzed by no less than thirty-one presumably homogeneous enzymes, not to speak of the several coenzymes active in some individual systems of the cycle, or of the cytochrome systems of dehydrogenases which are concerned with activation of respiratory oxygen and easily raise the total number to 40 (Fig. 1).

[1] Baldwin, *Dynamic Aspects of Biochemistry*. Macmillan, New York, 1947.

It is obvious that a drug which interrupts the catalytic action of one of these forty dehydrogenases may stop completely the reactions of the whole metabolic cycle if the inhibited enzyme happens to be located at a strategic position. There are, however, among these dehydrogenases a few factors which catalyze outlying processes and which have no immediate bearing on the essential steps of the cycles. Also, several of the dehydrogenases even within the cycles can be by-passed if necessary without seriously impairing the operation of the remaining steps. A drug which selectively affects such less vital catalysts should prove extremely valuable as a medicinal agent.

II. PHARMACOLOGICAL STUDY OF DRUGS

Deviation from the normal course of a biological process in animals and in man can arise from pathological changes of glands, nervous and muscular tissue, and other body organs. Restoration of normal conditions calls for surgery, mental therapy, or treatment with drugs which tend to alter the function of the diseased organs. Such drugs are called functional drugs or, because they influence the dynamics of physiological processes, pharmacodynamic agents.

If the derangement of the organs has been brought about by an infection, drugs to combat the causative infectious invader will be chosen. This is the field of chemotherapy. Some investigators now prefer to call all drugs chemotherapeutic agents, whether they are directed against infectious diseases or non-infectious disorders of body functions. This is purely a matter of definition and has led to some confusion in the classification of the vast field of medicinal chemistry. Arguments for and against this revision of nomenclature will be presented in the introduction to Chapter XXXI. For the purposes of this volume, the classification of drugs as pharmacodynamics and chemotherapeutics in the traditional sense will be adhered to.

Unless the pharmacologist allows a drug to react with pure compounds isolated from the tissues and known to play a part in the normal physiological processes he is about to influence by the drug, he will find it extremely difficult to interpret the overlapping varied actions of the drug he is studying. That holds even in the case of the inactivation of highly purified enzymes by drugs. In all other fields of experimental chemistry the conditions for a reaction are chosen as simple as possible. The organic chemist will rarely ever let two unrelated or slightly related reactions run side by side in the same reaction vessel. The physical chemist will choose the simplest possible conditions for his experiments and try to avoid complications by using relatively simple molecules, the pharmacologist is confronted with an extremely complex physiological system in which many reactions interlock and occur side by side, promoting or inhibiting each other.

An additional difficulty is the variation in even the same simple species

of individual cells under the influence of a drug. In contrast to a simple physico-chemical system no results in pharmacology are exactly reproducible. Therefore, only averages of several responses can be measured, and a series of experiments will always be required with control cells or organisms in order to provide a check on probable errors.

With so many variables at hand, the pharmacologist usually makes a qualitative study of a group of drugs in order to determine which of them is most active in producing a certain condition. However, it has been found more profitable to fix one variable, namely the degree of that response, and to apply a number of drugs in different dosages to reproduce the same degree of this reaction. Only in this way a quantitative comparison between drugs is possible, but even under the most favorable conditions it is difficult to obtain reproducible values. At best such data may have to be subjected to statistical analysis of a large number of cases before conclusions leading to clinical trial can be drawn.

Few pharmacologists will wish to establish for a compound only a certain qualitative activity, but one can evaluate the drug by administering it to an animal and observing, without even measuring the dosage level, its effect. Thus, a certain drug may lead to stupor, vomiting, excitement, weakness and other symptoms. A semiquantitative estimate is possible if only one variable is measured; the dose range which produces one or several of these effects is the most common variable chosen. The final quantitative measure is a combination of both the dose level and the degree of the observed symptoms.

After the establishment of qualitative and semiquantitative data, most pharmacologists proceed immediately to measure the acute toxicity of a drug in order to explore whether experimentation involving many animals and prolonged observation is justified. Should the drug be too toxic, further investigation will not be warranted unless the pharmacological behavior is exceptionally interesting.

The laboratory animals used in pharmacology are albino mice and rats, rabbits, guinea pigs, dogs, cats, hamsters and monkeys. For special fields, various species of birds or amphibious animals have been used.

The drug may be administered either by mouth (orally) or parenterally, by way of the circulation. The oral route of administration is wasteful unless a stomach tube is used, and gives less reliable values due to difficulties of systemic absorption. Injection may be given under the skin (subcutaneously), into a vein (intravenously), into a muscle (intramuscularly), or into the abdominal cavity (intraperitoneally). Other anatomical sites of injection have led to still other terms, such as intrathecal, intraspinal, intraventricular and intracisternal.

The instrument for the injection of a solution is a syringe attached to a hollow hypodermic needle. Lately, a new instrument, the hypospray, has made its appearance for the same purpose. In contrast to the hypo-

dermic needle, the hypospray shoots liquid under the skin or into the muscle without a needle. A combination of springs forces a thin stream of liquid of a diameter of less than 0.01 mm. under 1–5 atm. of pressure from a nozzle into the tissue. The force of the injection is too great to be useful for intravenous administration: the liquid passes through the vein.

This innovation could benefit especially those patients who must have repeated and frequent injections, such as diabetics who have to have insulin administrations several times per day. So far, however, it has proved difficult to inject accurately measured dosages with the hypospray.

On the whole, oral administration of a drug produces fewer, and often only delayed toxic symptoms as compared with parenteral administration because the drug has to be absorbed from the intestinal tract into the blood, and this process causes a lag in the start of the action of the drug and is, moreover, often incomplete. The best quantitative data on oral activity can only be obtained if the compound is completely, or virtually completely absorbed from the intestinal system and thus reaches the blood quickly and in a concentration similar to that resulting from parenteral injection. This is not easily achieved. When the drug is injected, the rapid circulation of the blood carries it to all parts of the body within a short time, and this route is therefore the standard method by which a new compound is tested in animals.

1. Absorption, Distribution and Excretion

The classical investigations on the absorption of drugs by cells were carried out by Meyer[2] and by Overton[3] fifty years ago. They showed that organic chemicals, which are to penetrate the membrane of the protoplasm, must have a certain ratio of solubility in lipids and water. The conclusion drawn from these experiments was that the plasma membrane was lipid in character, and led to the construction of model membranes (water-ether, oleic acid-diamylamine, cholesterol-water, etc.) to obtain distribution coefficients *in vitro*.[4] Since these studies were largely concerned with the transport and absorption of narcotics, a more extensive discussion of their details will be presented in Chapter VII. They have been strengthened by the finding that the membranes of red blood cell "ghosts" whose hemoglobin has been removed consist mainly of protein (1 part) and a system of phospholipids and cholesterol (0.59 part).[5] The phospholipids are perhaps present as insoluble complexes with basic proteins.[6] Absorption across a membrane may be simply a process of diffusion depending

[2] Meyer, *Arch. exp. Path. Pharmakol.*, **42,** 109, 119 (1899).
[3] Overton, *Arch. ges. Physiol.*, **92,** 115 (1902).
[4] Nirenstein, *ibid.*, **179,** 233 (1920).
[5] Parpart and Dziemian, *Cold Spring Harbor Symposia Quant. Biol.*, **8,** 17 (1940).
[6] Chargaff and Ziff, *J. Biol. Chem.*, **131,** 25 (1939).

largely on the solubility of the compound (passive absorption), or it may be accompanied by a chemical reaction (active absorption). The absorption of glucose through animal membranes after phosphorylation is a well-known example of active absorption. It has been suggested that drugs which structurally resemble natural metabolic products are transported through membranes by similar processes as their natural analogs.

Adequate solubility in both lipids and aqueous cell fluids cannot account for the absorption of all compounds through membranes. Water-soluble materials without a semblance of fat-solubilizing functional groups have been known to penetrate into mycobacteria which, even though they may not be encapsuled in a lipid membrane, undoubtedly contain a high amount of lipid matter. For such cases, a sieve-like membrane with pores has been visualized through which compounds with appropriate molecular volumes could pass. The nature of other bacterial membranes is probably also lipid.[7]

Absorption of ionizable substances has been found to occur preferably in the unionized state, although the ion shows frequently higher activity after penetration into the plasm. This has been observed for local anesthetics, hypnotics and chemotherapeutics.

Absorption implies admission of a drug not only to the circulatory fluids but also to various tissues whether or not they are perfused adequately by the circulation. The less the perfusion the greater the chance for localization of the drug in the tissue. Apart from these purely mechanical considerations of transport, the properties of the compound itself determine its distribution in the tissues. It has been shown that for some drugs there is a relation between their degree of ionization and their distribution. However, this does not hold for all drugs even in a related series, and purely structural factors enter into this picture.

Absorption studies would be incomplete without subsequent inquiries into the fate of the drug by excretion. Excretion in the feces needs to be considered only for poorly absorbed materials which had been administered with the food and failed to pass through the intestinal wall. Renal excretion is of greater importance since it reduces the concentration of the drug in the blood, influences its distribution in the tissues and shortens the therapeutic activity of the compound.

In the kidney, the majority of the drugs or their metabolic products pass into the urine by ultrafiltration through the glomerulus but many are reabsorbed into the blood completely, or in part, by the tubules before the urine is excreted. The rate of excretion can be altered by drugs which affect renal functions. Diuretics hasten excretion while drugs which block tubular excretion have the opposite effect (Carinamide, Chapter XXXVIII).

[7] Davson and Danielli, *The Permeability of Natural Membranes*. Cambridge Univ. Press, London, 1943.

Enteric Coating of Drug Tablets

The physiological advantage obtained by administering to a human patient a drug by the oral route, instead of parenterally, is counterbalanced by the problem of establishing therapeutic blood levels of the compound by speedy absorption. Moreover, even if we deal with a drug which passes unchanged by the digestive juices and is absorbed chemically unaltered, repeated administrations of the drug may be required in order to maintain effective blood concentrations. This presents a practical problem of no small importance in clinical medicine, since a patient may have to be aroused several times at night to receive the drug, and may thus lose the undoubted therapeutic value of natural sleep.

Various means of evading the necessity of repeated administration of small doses have been proposed. Once consists of chemical alteration of the drug to a derivative which remains in the system, and is slowly reconverted to the active material by the body fluids. The effect of a well-functioning male sex gland can be simulated by administering (parenterally) testosterone propionate; the ester is hydrolyzed slowly by the slightly alkaline blood, and the net effect is a slow release of small amounts of the hormone.

A second mode of administering (orally) several small doses in one tablet makes use of enteric coating. The drug is encased in a capsule which reacts with the digestive juices at given intervals, and thus makes available successive dosages for absorption. Enterically coated tablets have been constructed in different ways. Some capsules consist of alkali soluble polymers (polyacrylic acid, cellulose acid phthalate, etc.) which do not dissolve in the acidic gastric juice. Alternately, the drug may be pressed between various layers of the enclosing plastic which have been chosen to be stable to different conditions of moisture, acidity or alkalinity. Slowly excreted drugs are unsuitable for this type of administration, as are those which are poorly absorbed from the lower intestinal tract. Highly toxic drugs, or drugs needed in massive doses cannot be coated enterically either.

2. Toxicity Studies

No drug exerts desirable actions exclusively which can lead to its use in therapy. The undesirable actions of a drug cover any kind of injury to tissues and are usually spoken of as the toxicity syndrome of the substance. The ideal therapeutic agent should exhibit a minimum of toxicity. If conditions simulating those in human disease are to be attained in the animal laboratory, one should really use for toxicity experiments animals which have previously been made sick. However, most pharmacologists prefer to use normal animals in their toxicity studies. This

eliminates the complications arising from aberrations from normal physiological events as they are caused by disease. Irritations and allergies produced by drugs are less frequently encountered in healthy animals.

In determining the acute toxicity of a drug, the pharmacologist administers the highest tolerated dose which is close to the minimum toxic dose, and counts the number of survivals and deaths of his animals, after one or repeated administrations. Another working method which produces a more graded response consists of observations of change in body weight, degree of response to stimulation and similar conditions in several individual animals. A good average in these measurements can be obtained only from a large number of animals. The so-called median response corresponds to the effect produced in 50% of the animals tested, the median lethal dose to the amount of drug which kills one-half of the test animals; it is designated as LD_{50}. Other designations are the median lethal blood concentration which kills only 50% of the animals (LBC_{50}) and expresses the LD_{50} as a percentage of the drug in the blood. This average value is more easily reproducible than the absolute observations of a given number of animals.

The LD_{50} cannot always be read directly from the experimental data, particularly when only limited quantities of the drug are available and tests in large numbers of animals are prohibitive. It can then be calculated from a formula devised by Kärber[8] where Xo is the logarithm of the dose

$$\log LD_{50} = X_o - \int \frac{d(p_1 + p_2)}{2}$$

killing all animals, p_1 and p_2 are the proportions of animals killed by two different doses (y and z), and d is log y minus log z.

The therapeutic ratio or index of a drug expresses the ratio of the minimum effective dose (MED) to the maximum tolerated or minimum toxic dose (MTD) usually in 50% of the animals used (MED_{50}, MTD_{50}):

$$\text{therapeutic ratio} = MED_{50}/MTD_{50}$$

For special conditions, alternate terms are used. In chemotherapy, it is spoken of as the chemotherapeutic index, or even more specifically, the antibacterial, the antimalarial index, etc.

Since laboratory animals obviously cannot describe their condition, it is important to determine toxicity in several different ways so that the drug can be compared with other compounds as accurately as possible. This holds particularly for comparisons of the concentration of the drug in the blood which afford proper evaluation after systemic distribution and which are necessary to produce the same therapeutic or toxic effects in different animal species.

[8] Kärber, *Arch. exp. Path. Pharmakol.*, **162,** 480 (1931).

A comparison of the maximum tolerated and the minimum effective dose can be effected only after a study of the chronic toxicity of a compound. This is done by subjecting healthy laboratory animals to the effects of a drug over a period of several months. The results obtained from these studies forecast the possibility of evaluating the action of the drug in man where it may have to be used for prolonged periods and should not exert any untoward effects on normal physiological functions not concerned with the treatment.

While not as many animals are necessary in the determination of the chronic toxicity as in the determination of acute toxicity, a careful study of their behavior while under the influence of the drug is necessary. These observations include measurements of their weight, the condition of various external organs, their general health, their protein intake, and examinations of their blood. Animals which die during the measurement of chronic toxicity are necropsied and carefully examined for pathological changes of their organs, and the survivors of the experiment are usually subjected to a similar procedure. The conclusions drawn from these observations will guide the clinician in his first experiments in man who, owing to the greater differentiation of his organs will respond to toxic doses of the drug more violently and eloquently than animals.

The actual observation of toxic symptoms belongs clearly in the realm of pharmacology and clinical experimentation. Unfortunately, barely any overall information concerning the relation of structure and toxicity has become available to guide synthetic ideas of the chemist. In the discussions of individual drugs, pertinent toxic symptoms will be mentioned but such purely qualitative descriptions are subject to wide variations and should not constitute a prejudice in favor or against a certain drug.

Toxic side-effects of a drug are usually accepted by pharmacologists with a measure of fatalism. Few theories relating toxicity and chemical structure have been proposed, perhaps for this reason. An approach to this question, basing toxicity on thermodynamic activity in a given homologous series, has been presented in Chapter III.

3. Metabolic Studies

It is important to know the fate of the drug in the organism. Compounds which are not changed along their metabolic path are sometimes physiologically inert. If the compound, as is usually the case, is changed chemically in the body it is necessary to investigate its metabolic reaction products. They may constitute the actual drug exerting the desired pharmacological action. Moreover, the metabolic products often have a toxicity different from that of the drug originally administered. It may be that instead of the "drug" given to an animal, its metabolic product should be chosen as the ultimate therapeutic compound. Therefore the study

of the excretion of a chemical and also of the mode of its excretion through the kidney, intestine, skin or lungs is of great importance.

One of the first tasks in the investigation of a drug is to develop a good analytical procedure for tracing minute amounts of unchanged drugs or of some of its metabolic products in the excretion of the animal. An excellent discussion of this phase of pharmacological investigation as used in the study of sulfa drugs but applicable to any drug, may be found in an article by Litchfield.[9]

Further pharmacological studies of a drug involve investigations of pathological changes brought about by planned alterations in the organs of the laboratory animal. Extirpation of glands or the brain, alteration of nerve paths and of the circulatory or gastro-intestinal system, followed by treatment of the animal with the drug are included in such experiments and will shed light both on the fate and the localities of the action of the drug in the animal body. Labeling of atoms in the molecule of a drug with isotopic or radioactive substitutions provides a modern and convenient method for following the fate of the compound in metabolic processes.

III. CHEMOTHERAPEUTIC TESTING

If a drug is to be screened as a potential therapeutic agent for an infectious disease, it may be tested first *in vitro* (in the culture of the test organism), or directly *in vivo*, in an infected animal. Several laboratories in this country have adopted the policy of testing one and the same drug against a dozen bacterial, protozoan and virus infections as well as against functional disorders, if the structure of the compound makes activity likely. It is obviously more difficult to carry out such a program than to test many drugs against only one infection or disorder since this involves fewer variations of experimental procedure.

1. *In Vitro* Tests

If possible, the organisms against which activity is to be tested, are cultured in test tubes containing a liquid medium, or on agar cup plates, and a drug is added to the culture. *In vitro* tests may also be combined with *in vivo* methods, as in the test in which the culture is placed on the chorio-allantoic membrane of the chick embryo; this procedure has been used in experimental tubercular infections.

The bacteriologist adapts the composition of the nutrients and the pH of the test medium, its temperature, and the duration of incubation to the species and strain of the test organism. The organisms themselves can be chosen to some extent according to the preference of the investi-

[9] Litchfield, in Northey, ed., *The Sulfonamides and Allied Compounds*. Reinhold, New York, 1948, p. 434.

gator.[10] It largely depends upon his intuition whether he will test a compound primarily against hemolytic streptococcus, pneumococcus, meningococcus, gonococcus cultures, or against colon or tubercle bacilli. Thus, the activity of sulfonamides has been measured frequently against a special strain of β-hemolytic streptococci first, but in other instances *E. coli* has been used as the test organism.

On the whole, Gram-positive organisms (Chapter XXXI) are more susceptible to drugs than Gram-negative microbes. They owe this susceptibility to their content of magnesium ribonucleate which can be separated from a Gram-negative "cytoskeleton" by extraction.

Many bacterial cultures appear as turbidities in the test tubes or on solid agar culture plates. Slowing-down (inhibition) of the multiplication of the cultures by drugs is followed by bacteriostasis, terminating multiplication of the bacterial population. A decrease in the number of bacteria is spoken of as the bactericidal property of the drug. A decrease in normal multiplication rate (inhibition by the drug) is measured in the cultures by turbidimetric methods (see also Chapter XXXXII).

2. *In Vivo* Tests

It is not always easy to determine the bactericidal properties of a compound because these measurements involve the disappearance of subcultures derived from the killed bacterial population. As already pointed out, *in vitro* tests do not always reveal activity of a drug because the latter may have to be converted to the active drug in the living animal before showing activity. Therefore, many investigators prefer immediate *in vivo* tests. This method is used in any case as soon as *in vitro* activity has shown very favorable results. If the *in vivo* test shows unusually high activity, the compound may be recommended for clinical investigation provided its absorption, distribution, excretion and toxicity relations make it appear suitable for this purpose.

Some infections cannot be established in common laboratory animals, and other hosts may have to be used. Plasmodiases are studied best in fowl, certain trypanosomiases in larger domestic animals, ascariasis in pigs, etc. The animals are infected with the minimum number of the pathogens which produce disease and are treated with the drug from the moment of infection on. Other methods recommend a later onset of therapy after the infection has well developed; if the prophylactic properties of a drug are to be measured the animal is first treated with the drug, and infected only after a given time has elapsed.

The route of infecting the animal is of importance since the drug has to be absorbed and transported to the primary site of the infection. It is

[10] Henry, *Bact. Revs.*, **7**, 175 (1943).

always necessary to establish certain blood levels, both of the infection and of the drug, in order to produce the characteristic symptoms of the disease, and to be sure of a satisfactory concentration of the drug where it is most needed.

In many of the older experiments the investigators preferred *in vitro* methods because they involved less danger in handling highly virulent bacterial strains. When precautions are taken by sterilizing the laboratory air by ultraviolet light and similar devices, no undue danger to the operators need to be feared.

The virulence of the infection depends upon the frequency with which the test organism has been passed through an animal, as well as on mutation characteristics of the organism. A virulent infection is harder to combat with a drug than a less virulent one. The size of the infecting dose is usually chosen as a multiple of the lethal dose of the infectious parasites and is frequently expressed as the LD_{50}, that is, the dilution of the infectious suspension by which 50% of the animals are affected.

If oral activity of a drug is to be determined, the animal is usually fed the chemical several days before the infection in order to obtain therapeutic blood levels of the drug within a reasonable time after the infection. The maximum tolerated dose of the drug previously determined, is administered to the animal in order to provide the optimal therapeutic conditions. With many virulent strains the test animals die within 48 hours after the infection, and treatment for three days is, therefore, usually sufficient to determine whether or not a drug is active. Careful control by treatment of non-infected animals with the drug, and by infecting animals without benefit of subsequent drug treatment is necessary in all cases in order to check on variations in experimental procedure.

If survival time of the treated animals is measured it is compared with that of the controls or of the uninfected animals treated with a drug. More accurate values are obtained by recording the response from 50% of the infected animals.

In comparing *in vitro* and *in vivo* activities, we have assumed that a compound which is inactive *in vitro* is also inactive *in vivo* unless it is changed to an active drug in the body of the host. However, inactivity *in vitro* can also be caused by the presence of a large amount of drug antagonists. In the animal body where the drug antagonist is more highly diluted this influence would not be felt, and activity may be retained.

Activity *in vitro* does not guarantee activity *in vivo*. Failure to observe *in vivo* activity in drugs which have shown activity *in vitro* is often due to the toxicity of the compound which kills the animal before a therapeutic effect takes place. It is also possible that a drug is changed in the animal body to an inactive compound so rapidly that its activity is lost before it can be observed.

CHAPTER VI

Restricted Response of Cells to Drugs

The case history of medicinal chemistry abounds with examples of drugs which are inactive in the special biological condition in which they have been tested. It is indeed more often the rule than the exception to find a new or previously untried compound "physiologically inert." The endless series of chemicals differing from each other by slight systematic variations attest to the efforts of medicinal chemists to overcome this difficulty by trial and error.

A limitation should be put on the statement that so many compounds are biologically inert. They are usually not entirely inert, but rather do not produce the effect they have been tested for. Even such simple substances as water or sodium chloride may initiate far-reaching secondary physiological alterations by hydrating, denaturing and dehydrating macromolecular constituents of living cells. Most chemicals exert some physiological activity at proper concentrations and under suitable conditions. Many affect dozens of cell reactions, even though a beneficial and medicinally important reaction may not take place. Such compounds are said to exert undesirable side-effects, and are discarded and buried in the pharmacological literature, with a few unhappy remarks as their tombstone. This book has not attempted to exhumate but a few of them, and only those whose lack of activity has been of didactic value in pointing out dead-end alleys of medicinal research.

When a compound is inert in a given biological test, it does not react with those cell chemicals which should be affected. Thousands of substances do not react with each other in the chemical laboratory, and this picture is repeated even more often in the living cell. This condition may be called *natural resistance* to drugs.

An entirely different aspect is opened up if we find that a drug exerts a decided, and frequently beneficial action, and that this activity is suddenly weakened, lost, or even reversed after repeated application. We find innumerable examples of this puzzling phenomenon both in the literature of pharmacology and of chemotherapy. These observations have been made over a period of many decades by many investigators whose medical, bateriological and chemical background led them to multiple explanations of these phenomena, and to an unruly nomenclature by which they have tried to classify them.

The chemist, confused by these classifications, should remember that he is guilty of a similar offense. Who has not tried to look up a medium-complex organic compound by its IUC name, only to find that it is catalogued under a different system, if not even under one or two trivial names? The difference between the chemical and pharmacological multiplicities of nomenclature lies in the fact that the chemist uses here different names for the same compound, while few exact biological scientists will admit that by apparently coinciding names they wish to designate the same set of conditions. Their difficulty lies in the complexity of *in vivo* processes which comprise too many unknowns to be clearly definable. With this in mind, we may examine the different phases of developed restricted response to drug action.

I. TACHYPHYLAXIS

This phenomenon is restricted, by usage, to the group of sympathomimetic drugs and the hormones of the hypophysis. There are numerous cases on record in which an animal reacts to a second dose of the same drug in the reverse sense as it did to the first dose. For example, the first injection of a certain adrenergic drug produces a strong rise in blood pressure, while a later renewal of that dose in equal amounts may cause a drop in blood pressure. No satisfactory mechanism for tachyphylaxis has been proposed. Tachyphylaxis may become a permanent characteristic of the animal, and its response to the same drug at a later date may be nil or even the reverse of the expected reaction.

The term tachyphylaxis was created[1] to describe a particularly rapid onset of certain immunological phenomena. As long as any of the original dose of the same drug is still present in the body liquids, a second dose cannot cause a reaction with the "sensitized" organs. Histamine, the alkyl nitrites and certain colloidal solutions which lower blood pressure give occasionally rise to similar symptoms. Epinephrine fastness may be caused by an increase in plasma histamine which overcomes the effects of epinephrine.[1a]

II. HABITUATION

If it becomes necessary to readminister a drug at frequent and regular intervals in order to maintain a semblance of physiological equilibrium, the term habituation is in order. Habituation involves a certain degree of physical dependence on the drug, as it is found in habitual heavy tobacco smokers or the millions of people who develop a headache if they are de-

[1] Champy and Gley, *Compt. rend. soc. biol.*, **71,** 159 (1911).
[1a] Yonkman, Levinson and Segal, *Am. J. Digest. Dis.*, **17,** 149 (1950).

prived of their cup of coffee at breakfast. Psychological effects enter into this picture both in man and in animals.

It is characteristic of habituation that no increase in dosage is required to bring about the same reaction over long periods of time. Nor is there any occurrence of serious and dangerous withdrawal symptoms when the drug is withdrawn, although a certain amount of discomfort may follow the withdrawal of stimulants (caffeine, nicotine), sedatives (hypnotics), and other functional drugs such as habitual laxatives. In a sense, habituation which requires no increase in dosage to produce the same effect can be classified only loosely as restricted response to drugs.

III. TOLERANCE

The situation is different with drugs which produce tolerance. It is a condition related to habituation but requiring increasing dosages of the drug to produce the same effect. Humans and animals who have become tolerant to a drug are truly inert to the action of considerable and often dangerous doses of the compound. Amounts exceeding many times the certain toxic level in normal individuals can be taken by persons who have developed tolerance. Physical dependence is pronounced, and withdrawal causes disturbing physical symptoms of varying degree. The most serious withdrawal symptoms are observed in persons who have developed tolerance to morphine and other powerful analgetic and euphoric drugs. The state of such individuals is referred to as *addiction* (Chapter XI).

The causes of tolerance and addiction are not clearly understood. The drug undoubtedly affects originally the metabolic reactions of certain groups of cells, probably nerve cells, and the reactivity of the cell chemicals is dulled by prolonged and continued renewal of the inhibitory catalytic influence of the drug. Whether the concentration of reaction products from the interaction of drug and substrate decreases the reactivity of the latter, or whether other biochemical manifestations are at play has not yet been determined.

The interference of the drug with metabolic reactions of functional cells, and the slow loss of reactivity characteristic of tolerance are reminiscent of the phenomena observed in acquired resistance. The latter expression has been used almost entirely in microbiology, while tolerance has remained part of the terminology of pharmacology.

IV. ACQUIRED RESISTANCE

The term acquired resistance, or for short, resistance to drugs has been restricted largely to the field of chemotherapeutic agents. The phenomenon is characterized by an increasing refractoriness of parasitic cells against drugs which may terminate in virtually complete inertness to the

drug, or drug fastness. Resistance can be acquired slowly or fast, depending on the organism and the drug involved. Because at least bacterial cells can be cultured well in the laboratory, and because they can acquire resistance *in vitro*, the observations of this type of inertness to drugs have gone further than in other cases. It has been possible to follow metabolic changes in the cells concerned, and to evolve reasonable explanations of these processes.

A cell metabolizes its nutrients by using them as substrates in its enzymatic reactions. If the nutrient (the substrate) is changed, the cellular enzymes are forced to alter their specificity. Two types of variations of enzymatic activity have been studied. The first one, a rapidly occurring, and rapidly reversible variation in enzyme response has been defined as variation by enzyme adaptation.[2] It cannot be caused by a radical change of enzyme structure, but has been explained by the presence of alternate enzymes in the cell which can take the place of the first, normally dominant, member of the system. These alternate enzymes are ordinarily dormant, either because their specific substrates are lacking, or because they have been inhibited by drugs. As their substrate is supplied in the altered medium, they adapt the cell to the new condition.

An example of this condition can be found in human physiology. After surgical extirpation of the stomach, the tissues which supply pepsin and other gastric proteases are no longer available. Nevertheless, a semblance of gastric digestion of foodstuffs can be carried on after a while, as similar, but not identical enzymes from other tissues take over the proteolytic duties of the lost catalysts.

The change is comparable to new approaches a chemist would employ in the course of a synthesis as new starting materials become available. The cell too has to do some new chemical "planning," but since no other change is involved, variation by adaptation proceeds without cell division.

The other type of adaptation, variation by selection, involves enzymes of new generations of cells produced by cell division, and is not induced by the sudden availability of new nutrient substrates. It endows the existing enzymes with permanently altered catalytic activities and is thus inheritable. If this change occurs in all cells of a bacterial culture, the organisms will present the picture of mutation. In recent years, evidence has grown stronger for the assumption that certain drugs can influence the arrangement of chromosomes in plant and animal cells. This holds not only for such well-known examples as colchicine which has a direct effect on nuclear division. A study by Emerson and Cushing[3] has made it plausible that in the organism *Neurospora* true mutation occurs as

[2] Work and Work, *The Basis of Chemotherapy*. Interscience, New York, 1949, p. 244.
[3] Emerson and Cushing, *Federation Proc.*, **5**, 379 (1946).

an effect of complete adaptation to sulfonamide drugs. The mutants can also be produced by di-β-chloroethylamine, one of the nitrogen mustards (Chapter XXVII).

It happens that *Neurospora* can be analyzed fully by genetic methods. The same nitrogen mustard also produces alterations of bacterial strains which can be followed by studying the altered metabolite requirements of these variants. Bacteria do not propagate by sexual processes and the term mutation can be applied to variations of their strains only with some reservations. Nevertheless, the similarity of the effects induced in *Neurospora* and in bacteria by the same chemicals lends credence to the theory that in both types of cells analogous mechanisms are at work in producing daughter strains of the original cells with new enzymatic reactions.

A small percentage of colonies possessing natural resistance to a given drug may be expected to be present in any large bacterial population. The drug-fast strains so dreaded by the clinician arise by division of these cells after the multiplication of susceptible forms has been arrested by the drug, or else by the processes of adaptation discussed above.

It is interesting that drug-resistant bacterial daughter strains often also differ from their parent strain in their virulence, serological behavior, and even in their morphological appearance. This is additional evidence of the turn toward the inherited character of pronounced resistance, or, as t may be put, the inheritability of enzymatic alterations.

1. Resistance to Sulfonamide Drugs

When bacteria or other microorganisms are exposed to a sublethal but gradually increasing concentration of a sulfa drug, they can be trained to withstand the bacteriostatic action of these compounds and become "fast" to the drugs. Many drug-resistant strains have been developed by this procedure both *in vitro* and *in vivo*, and resistance to drug action can be retained by some strains even after 200 passages through animals. When an organism develops resistance to one of the sulfonamides it does not necessarily become resistant to all of them but its resistance to the other sulfa drugs is potentially increased. Consequently, it will be less readily attacked by them.

On the other hand, drugs which act on microorganisms by a different mechanism such as some of the antibiotics (penicillin, streptomycin, etc.) may still exert on the sulfa-resistant parasite the same action as on the non-resistant strain until the parasite becomes able to withstand the action of the antibiotic as well as that of the sulfonamide.

The importance of the clinical implication of resistance to sulfa drugs is obvious. In one gonococcus infection it was found that by culturing

the bacteria from the infected individual *in vitro* it was possible to predict whether clinical response to sulfa drugs could be expected in patients who would contract the disease from the original carrier. In other cases it was possible to foresee whether certain strains which were resistant to one sulfa drug would be susceptible to other therapeutically useful sulfonamides.

A possible mechanism by which a microorganism develops resistance to a sulfa drug may be based on the observation that bacteria exposed to sublethal doses of sulfonamide drugs become capable of using more efficiently the available *p*-aminobenzoic acid in their metabolism to overcome the effects of inhibitory medicinals. Strains have been encountered in which one mole of PABA originally antagonized 14 moles of sulfathiazole but for which, after development of drug resistance, 220 moles of sulfathiazole could be antagonized by the same concentration of PABA.

The organisms may also begin to synthesize more PABA in the presence of sulfa drugs in order to overcome the inhibition imposed on their PABA utilization, but this has been observed only with non-pathogenic bacteria. The possibility that bacterial cells trained to resist sulfonamide drugs become more permeable to PABA, and thereby draw it more efficiently out of the surrounding medium is supported by the fact that similar quantities of the metabolite have been found in both normal and resistant bacterial strains. Resistance *in vivo* follows the pattern of *in vitro* experiments.

Some organisms have demonstrated their ability to develop enzymes which can destroy bacteriostatic drugs such as penicillin, and to become resistant to antibiotics in this manner. Penicillin is toxic to most Gram-positive organisms but does not affect most Gram-negative and animal cells. A definite difference between Gram-positive and Gram-negative microorganisms is the ability of the latter to synthesize amino acids while Gram-positive cells draw them largely from the surrounding medium by a process of assimilation. Gale and Taylor[4] found that penicillin inhibits the uptake of glutamic acid, and they believe that the death of the cell is initiated by this mechanism. On the other hand, a staphylococcus strain trained to resist the antibiotic lost its need for glutamic acid which the drug-sensitive parent strain had to have if it were to live. It actually began to synthesize its own glutamic acid. Moreover, addition of ribonucleic acid increases bacterial resistance, and this is in accord with the content of magnesium ribonucleate in bacteria which are not attacked by penicillin.[5]

[4] Gale and Taylor, *Nature*, **158,** 676 (1946); *J. Gen. Microbiol.*, **1,** 314 (1947).
[5] Gale and Rodwell, *J. Bact.*, **55,** 161 (1948). George and Pandalai, *Lancet*, **1,** 955 (1949).

2. Resistance to Streptomycin

The resistance of pathological organisms to this antibiotic follows the pattern discussed under 1. Resistance to streptomycin and dihydrostreptomycin develops with great regularity and with considerable speed. It may be responsible for the relative ineffectiveness of streptomycin in tuberculosis and related infections. A number of other antibiotics now in clinical use seem to produce resistance much more slowly than streptomycin.

Mycobacterial strains have become known which appear to be able to utilize streptomycin as a nutrient, and flare-ups of such infections immediately after treatment with streptomycin have been observed.. Many clinics now test bacterial strains from patients for resistance before instituting antibiotic treatment.

3. Resistance of Trypanosomes to Drugs

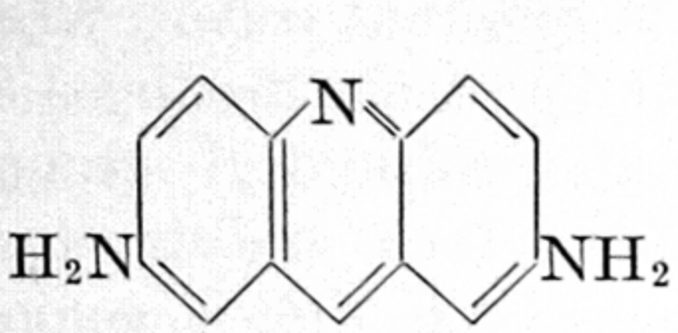
Studies on drug resistance in trypanosomes are treated here separately although there is no reason to believe that mechanisms differing from those encountered with bacteria are at work in these protozoa. However, it has been barely twenty years since trypanosomes have been cultured *in vitro* for even such short periods as one day without profound morphological changes.[6] Therefore, most investigations in this field have been carried out with experimental trypanosomiases in animals, and the observations have been clouded by the complications of the host system.

Trypanosomes are so difficult to culture outside the host cell because they have adapted themselves considerably to the metabolic aid of the latter. In the course of millions of passages through the host, trypanosomes have lost a large number of enzyme systems and have become dependent on the cells of their host. Pathogenic trypanosomes can barely oxidize glucose to CO_2, have no oxidizable reserve materials and cannot respire unless oxidizable substrates are added. Under physiological conditions, they do not hydrolyze proteins, and their respiratory enzymes are not poisoned by cyanide.[7]

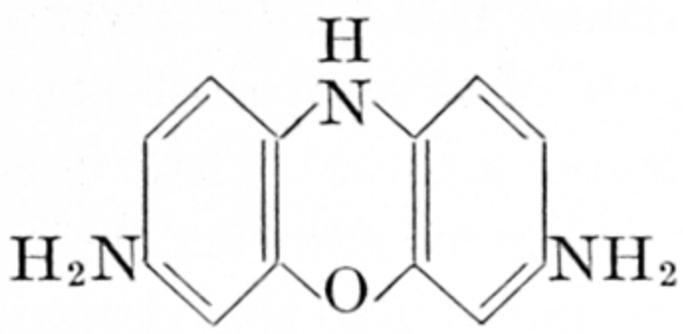
The first recognition of drug resistance in trypanosomes came from Ehrlich's work on chemotherapeutically active dyes. The phenomenon was observed readily because organisms which had acquired resistance could no longer be stained by the particular dyestuff. In this way, Ehrlich discovered resistance of *Trypanosoma brucei* in mice to triphenylmethane dyes. He noticed that strains resistant to parafuchsin were also refractory to other triphenylmethane dyes, but not to azo dyestuffs or to organic

[6] Yorke and Murgatroyd, *Ann. Trop. Med. Parasitol.*, **24,** 449 (1930).
[7] Moulder, *Ann. Rev. Microbiol.*, **2,** 114 (1948).

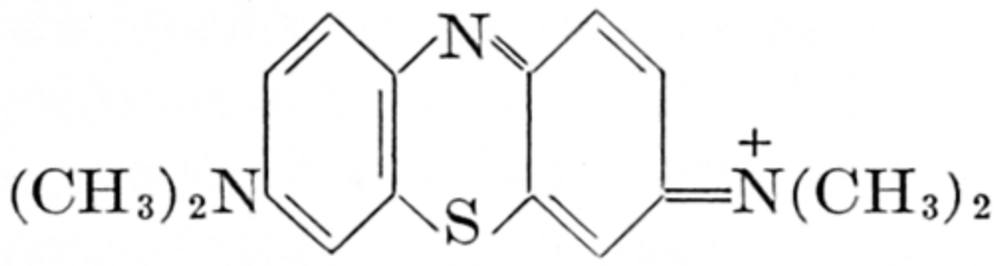
arsenicals. Resistance to dyes in the acridine (VI-1) series overlapped with resistance to structurally related oxazine (VI-2) and thiazine (VI-3) dyes.



(VI-1)



(VI-2)



(VI-3)

Trypanosomata can readily acquire resistance to arsenical drugs. They concentrate ("fix") the drug in the parasite cell by absorption from the surrounding medium as long as they are susceptible to the agent. This preferential process of absorption is apparently responsible for the selective toxicity of arsenicals to the parasite in the animal host. As they acquire resistance, the trypanosomes shed their ability of absorbing the drug from their environment.[8]

The arsenoxides (ArAsO) are the effective agents against trypanosomiases, and other valence forms of arsenic have to be oxidized, or reduced to this stage before the parasites can be poisoned. That the cells of the host have the function of carrying out these oxidations or reductions is evident from the inactivity of many arseno compounds and arsonic acids *in vitro* which, in the living animal, have therapeutic activity. It could barely be assumed that the trypanosomata would perform this suicidal chemical mission, unless the enzymes have become refractory to arsenoxides.

A similar case of self-protection exists for bacterial cells which do not reduce the azo dye Prontosil to sulfanilamide; here too the host has to carry out the reductive cleavage, and the dyestuff is active *in vivo* only.

As it will be pointed out in the description of BAL (Chapter XXXII), the arsenoxides react with sulfhydryl groups of enzyme systems, and this reaction can be prevented, or at least minimized by protection of the parasite with dithiols which bind the arsenic atoms in stable five-membered rings. As resistance develops, it can hardly be expected that the number of -SH groups of the parasitic enzyme systems (insufficient as these are) should have decreased to the point where there would be no longer enough of these groups for reaction with trivalent arsenic atoms. If this would

[8] Voegtlin, Dyer, and Miller, *J. Pharmacol. Exptl. Therap.*, **23,** 55 (1924).

be so, the cell should also have lost its capacity for many important metabolic processes which are generally dependent on sulfhydryl groups, but there is no sign of diminished metabolic activity in resistant cells. While the final trypanocidal effect of arsenical drugs is undoubtedly produced by the combination of arsenic atoms with enzymatic sulfhydryl groups, resistance against these drugs is not directed against their arsenic atom, but against their ability to penetrate the trypanosomal cell, that is, against their absorption.

The properties of arsenicals which make the drugs absorbable are governed by the chemical structure of the compounds. Differences in absorption and distribution depend on differences of physical properties of the individual drugs. Resistance must develop, therefore, against the effects of functional groups of the drug which endow the compound with the correct distribution coefficient to penetrate parasite cells under ordinary circumstances. One can visualize that the enzymes along the trypanosomal membrane change the shape of their polypeptide chains in such a manner that groups usually on the outside, and thereby receptive to the functional groups of the drug, are hidden inside the folds of the protein molecule. It is probable that resistance to other trypanocidal agents such as Suramin is developed by similar alterations of absorption characteristics.

CHAPTER VII

General Anesthetics

I. INTRODUCTION

Anesthetics are drugs which depress vital functions of all types of cells but especially those of nervous tissue. Depending partly on the site of application, an overall classification of anesthetics can be proposed. General (central) anesthetics depress the central nervous system to such an extent that all sensitivity to pain is lost, and the individual suffers a hiatus of consciousness. If applied to specific structures of the central nervous system, particularly the spinal fluid, certain anesthetics block impulses transmitted by nerve fibers emanating from the region involved, and may be used in "spinal anesthesia" for the insensibilization of organs served by that innervation. Where only peripheral nerve endings are involved, the local anesthetics are applied directly to a restricted area for the obtusion of pain.

The general anesthetics may be subdivided into volatile or gaseous compounds which are administered by the respiratory route, and the fixed anesthetics. The volatile anesthetics enter the blood stream by way of the lungs and reach quickly the central nervous organs which are transfused by a large amount of circulation. The rest of the body is affected more slowly since the tissues receive the necessary anesthetic concentration only after some time. It therefore forms a huge buffer system, withdraws the anesthetic only slowly from the brain, and retains it more consistently even after the brain tissue has given up its anesthetic when the source of external supply has been removed.

The fixed anesthetics are non-volatile drugs which may be administered by injection, or by way of the alimentary canal. They have a predilection for the central nervous organs where, after being deposited by the circulation, they enact their depressant effect.

The anesthetic effect produced by any of these drugs, whether central or local, is reversible, and the affected organs return to a normal state after the concentration of the drug has been decreased below the threshold of its effectiveness.

A clear-cut definition of the different types of anesthetics is difficult to obtain since their effects may overlap. Moreover, a "depressant" action is part of the mechanism of many therapeutics, and the main virtues of the central anesthetics, insensibility to pain and loss of consciousness, are found to some degree in the analgetics and hypnotics, respectively. Vice versa, minor doses of certain anesthetics cause analgesia by a central mechanism, and the occurrence of post-operative sleep, caused by the slow disappearance of a volatile anesthetic from the tissues, transgresses the irregular border line of hypnotic effects. Investigation of anesthetics has therefore been forced to focus attention on the main goals of surgical anesthesia, and to regard other effects as incidental, although occasionally as desirable.

The term anesthesia was coined by Oliver Wendell Holmes in a letter to William T. Morton, the discoverer of ether anesthesia for surgical purposes. It is derived from the Greek and means "without perception". The beginning of its usage followed the introduction of ether by Crawford L. Long of Athens, Georgia, in 1842, and that of nitrous oxide, the long known "laughing gas", by Wells and Morton in New England. Since other types of depressants such as the hypnotics also produce a condition resembling sleep and partial insensibility to pain the particular effect produced by the anesthetics is sometimes also called narcosis.

II. THEORIES OF ANESTHESIA

It is not surprising that the mechanism of anesthesia has not been explained satisfactorily if it is considered that no explanation for the physiological function of normal sleep has yet been discovered. Apart from various organic chemicals, certain ions, and different physical conditions can depress the central nervous system. They are fatigue, cold, lack of oxygen (anoxia) and the influence of potassium, magnesium and bromide ions. A careful study of organic anesthetics has revealed that the course of their action and their final physiological symptoms are not identical. From this it might be inferred that the mechanism of their action is not the same. However, a number of investigators have studied the influence of anesthetics on isolated groups of cells and have drawn conclusions which can explain anesthesia in general terms. Because of the relatively simple conditions of the *in vitro* experiments with anesthetics, these experiments have been used to interpret also other types of cell depression such as the bacteriostasis of sulfonamides.

Since blood is the vehicle to transport anesthetics from the lung and other points of entry to the central nervous organs and to other parts of the body, many *in vitro* experiments have been performed in this medium. As many of the theories of anesthetic action are concerned with the specific

solubility of the anesthetic drugs in certain cellular constituents, anesthetics have often been applied to isolated blood. The cells may then be centrifuged, and the anesthetic content of the cells measured by various methods. Because of the apparently low solubility in water and their high solubility in lipids, the theories concern themselves primarily with the solubility of anesthetics in intracellular lipids.

Application of an anesthetic to a cell would necessarily result in certain physical and chemical changes in the cell such as the permeability of the cell membrane, the surface tension and viscosity of cell constituents, and other colloidal phenomena. It is possible that the anesthetics interfere with oxidative processes of the cell by modifying the ability of the cell to utilize oxygen. Physical phenomena such as a change in the electric properties of brain cells from the observed normal may also have a part in anesthesia.

1. The Overton-Meyer Theory

One of the most widely accepted theories for the explanation of anesthesia is that by Meyer[1] and by Overton. It implies that the potency of an anesthetic drug is related to the relative solubility of the compound in water and in lipids. A true anesthetic is a chemically inert drug which is not readily destroyed, or eliminated from the organism, and is absorbed preferably by cells containing a large amount of lipids. In order to be transported to these cells, an anesthetic must also be soluble in water, but usually less than in the lipids of the cell. The proportion of the solubility in moles for a given quantity of lipids to that of an equal volume of water is called the distribution coefficient between oil and water. The higher the numerical value of this quotient, the higher should be the anesthetic activity of the compound. This is not always true; many substances having a high solubility in lipids and a low solubility in water, and therefore a high distribution coefficient, are not effective anesthetics.

The distribution coefficients may be obtained experimentally by dissolving a weighed amount of a substance in a known volume of olive oil, shaking the solution with a certain volume of water, and determining the weight of the drug in the two separated liquids. The quotient has also been calculated from the separate solubility data of the compound in water and in oil, but the values obtained in this manner are not necessarily correct. Since many distribution coefficients have been determined at 20° *in vitro*, care must be taken in applying the values to the *in vivo* conditions at 37.5° because of differences in solubilities at these temperatures.

[1] Meyer, *Arch. exper. Path. Pharmakol.*, **42,** 109 (1899); **46,** 338 (1901). Overton, *Arch. ges. Physiol.* **92,** 115 (1902).

Since olive oil is a rather crude model material for the lipid constituents of nervous tissue, the distribution of an anesthetic between water and a xylene solution of cholesterol should give a better picture of *in vivo* conditions. Even though cholesterol is a major lipid component of brain cells, this system does not provide for the ever present simultaneous transfer of ions across cell membranes. Substitution of a mixture of oleic acid and diamylamine for cholesterol in some experiments has been used to circumvent this objection.

TABLE I. DISTRIBUTION COEFFICIENTS OF COMMON ANESTHETICS

Cyclopropane	65	at	35°
Ethylene	13.2		18°
Chloroform	32		18°
Vinyl ether	8		18°
Ethyl ether	4.5		18°
Nitrous oxide	2.2		18°

The values listed in Table I coincide with the observed clinical effectiveness of the repective anesthetics. For a given anesthetic, its effective concentration in lipids in moles per liter is constant as observed from the solubility in olive oil, and the simultaneous determination of the narcotic concentration in mice and in frogs. An argument raised against the lipid theory points to the composition of nervous tissues; only half of the solids are lipids, while up to 90% of the total nerve consists of water. Moreover, the brain in the intact animal is perfused by a large amount of circulatory fluids and thus receives a higher concentration of the anesthetic than other tissues with a poorer circulatory system.

None of these experiments and theories explain the actual mechanism of anesthesia but only stress the affinity of lipid-containing cells for the drug.

The Meyer-Overton theory is most readily applied to aliphatic compounds while aromatic derivatives with a high distribution coefficient have frequently no anesthetic value. It predicts satisfactorily the observation that in a homologous series the permeability of a cell increases proportional to the molecular weight of the substance. Hydrophilic groups may be expected to lower anesthetic properties, and among the alcohols, the penetrability actually decreases with an increase of the number of hydroxyl groups. The number of polar groups is also inversely related to penetration. Tadpoles can survive a considerable time in a very dilute aqueous solution of strychnine nitrate but addition of sodium bicarbonate

to weakly alkaline reaction causes the animals to die.[2] On the other hand, certain atomic groups seem to affect cell permeability in an unexpected manner. Thus, amides with the same number of carbon atoms as alcohols of related structure permeate biological membranes more slowly than the hydroxylated compounds. The anesthetic inertness of many water-insoluble, and lipid-soluble alkaloids, ureides and other non-volatile compounds is also hard to fit into the picture of the Meyer-Overton theory. It may be that the observed relation of anesthetic activity to the ability of the drug to lower the surface tension of the cell has not been considered adequately in these cases.

2. Colloid Theories

Regardless in which way an anesthetic penetrates into a cell it will set up a number of chemical and physical changes within the cell which will affect many colloidal processes. Claude Bernard,[3] and later Bancroft[4] pointed out that the cell colloids may aggregate during anesthesia, and that this process, like many other colloidal processes is reversible and permits recovery. There is not much evidence for this theory. However, examination of cells capable of fermenting carbohydrates shows typical Brownian movement which stops after treatment with an anesthetic drug such as ether or chloroform. During the contact with the anesthetic flocculation occurs but peptization takes place after the anesthetic has been washed out. Fermentation of carbohydrates is resumed, as is multiplication of the cells.

3. Anesthetics as Enzyme Inhibitors

The role of anesthetics as enzyme inhibitors has been studied by Quastel.[5] In the concentration in which they produce surgical anesthesia many anesthetics inhibit the aerobic oxidation of glucose, lactic and pyruvic acid by brain tissue while anaerobic glycolysis is not affected. Likewise, oxidation of succinic acid is not decreased by anesthetics. Table II lists the oxygen quotients (QO_2) of brain tissue, that is the cubic meters of oxygen per milligram wet tissue absorbed per hour, and the percentages by which this quotient is cut down by phenobarbital, and by ether.

The exceptional position of succinic acid among the other metabolites

[2] Jacobs, in E. V. Cowdry, ed., *General Cytology*. Univ. Chicago Press, Chicago, 1924.
[3] Bernard, *Leçons sur les anésthetiques et sur l'asphyxie*. Baillière, Paris, 1875.
[4] Bancroft and Richter, *J. Phys. Chem.*, **35,** 215 (1931).
[5] Quastel, *Physiol. Rev.*, **19,** 135 (1939).

affected by anesthetics implies that the drugs cause differences in the metabolism, that is, in enzymatic activity of brain tissue. In the common scheme of biological oxidation the carriers of oxygen may be arranged in the following sequence: oxygen; cytochrome oxidase; cytochromes a, b and c; the flavoproteins; the pyridine nucleotides; a cortical dehydrogenase; and finally the substrate.

It is known that succinic acid does not need the cytochrome oxidases for its dehydrogenation to fumaric acid. Since the oxidation of succinic acid is unaffected by anesthetics it may be concluded that the drugs do not inhibit the cytochrome oxidases and cytochrome a, b and c. Indeed, cytochrome c can take up oxygen in the presence of narcotics; however, it cannot release it again as long as the drug is present. If methylene blue is substituted as a by-pass for the pyridine nucleotides, its reduction is inhibited by anesthetics. This points to the pyridine nucleotides as one group of carriers inhibited by anesthetics, but the flavoproteins are probably most severely affected. In any case, the inhibition of dehydrogenases by anesthetics is now well established.

III. THE BRAIN AND THE NERVES

Why should the brain and the central nervous system be the first tissues to be attacked by an anesthetic? The reason for this phenomenon may be sought in the high susceptibility of the brain to lack of oxygen; the brain, and especially the cerebral cortex, consists of more cells than all the rest of the body together and is abundantly supplied with blood. The kidney is the only organ perfused by a larger volume of blood in the unit of time. Equilibrium of brain receptors with the concentration of the anesthetic in the blood is thus reached rapidly. Finally, nerve cells and other constituents of the nervous system are more readily affected than the effector organ, that is, the muscle fiber or gland cells which are governed by the nerve.

TABLE II

QO_2	Brain tissue	Per cent QO_2 cut down by	
		Ether	Phenobarbital
Normal	2.89	—	5
+ glucose	12.20	52	55
+ lactic acid	13.55	32	35
+ pyruvic acid	11.10	29	27
+ succinic acid	9.53	—	—

1. Nervous Structures

A brief description of nervous structures may facilitate an understanding of anesthesia. The unit of nerve structures, the neurons, are classified as afferent, or sensory, if they lead from sense organs to nerve centers. Efferent, or motor nerves, pass from the nerve centers to the effector organs which are located in muscles (neuromuscular or myoneural junctions) or glands (myoglandular junctions).

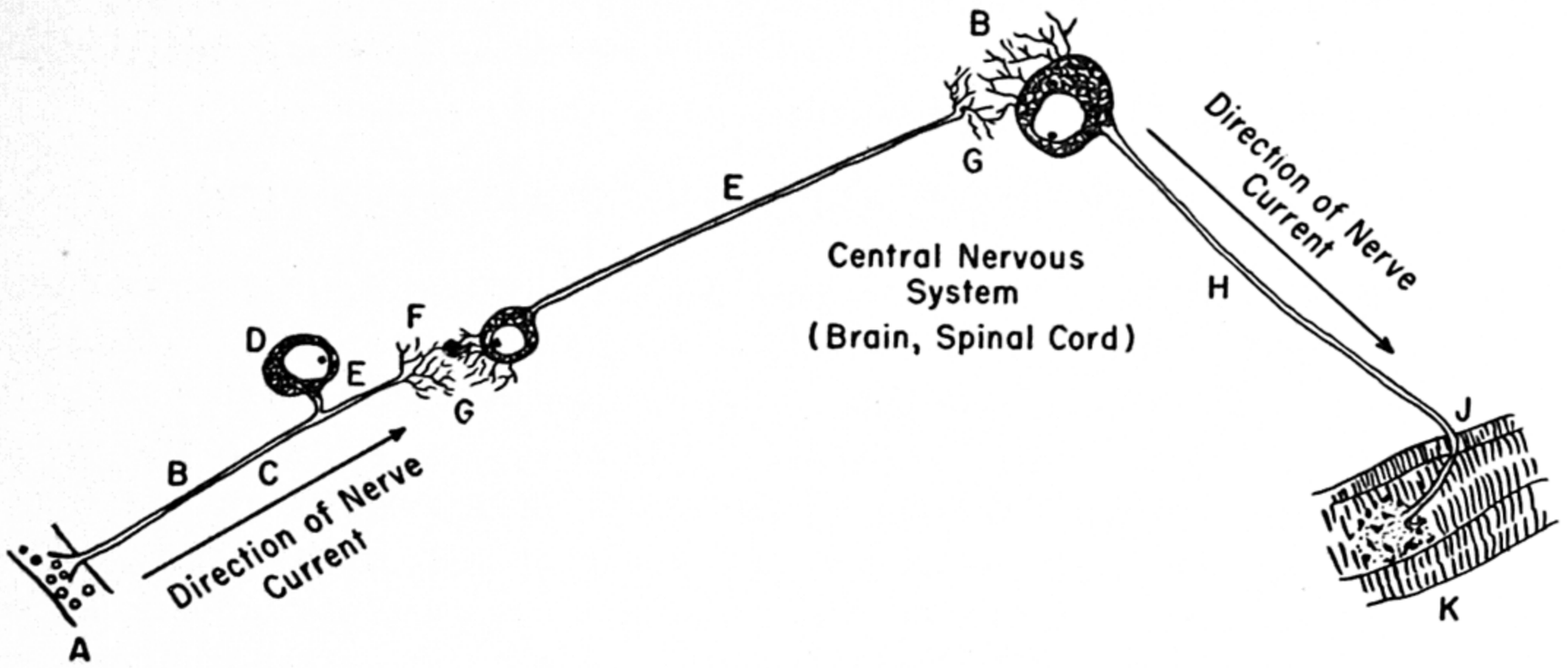


Figure 1. Schematic Drawing of Nervous Transmission

A, Receptor organ
B, Dendron
C, Afferent (sensory) neurons
D, Nerve cell body
E, Axon
F, End brush
G, Synapse
H, Efferent (motor) neurons
J, Myoneural or neuroglandular junction
K, Effector organ (muscle or gland)

Both afferent and efferent nerves consist of a basic element, the cell body. Two kinds of fibers emanate from the cell: the short and numerous *dendrites*, and a single *axon* which may vary from miscroscopic length to several meters. The axon terminates usually in several short branches, the "end-brush". Nerve impulses always pass from the dendrites through the cell and then through the axon. Although not actually physically connected, the axon end-brush of one neuron and the dendrites of another one are intermingled and the neurons are thereby arranged as a chain, the *nerve fiber*. The junction of two neurons is called a *synapse*.

The synapse, perhaps the most important part of the nervous system, is affected first by anesthetics, followed by the nerve cell in which the metabolic rate is sharply decreased. The neuromuscular junction at which the impulse is transferred from nerve to muscle is anesthetized next

with the nerve fiber, and finally the effector organs (muscles, glands) following suit.

At the synapse, acetylcholine stores energy in a metastable form and releases it as a sequence to the demand upon the neurons to transmit impulses (see also Chapter XXI). The energy needed in the synthesis of acetylcholine is obtained, in part, from the oxidation of body chemicals which also supplies acetate ions. The release of energy by hydrolytic decomposition of acetylcholine is catalyzed by potassium ions, and furnishes the means of transmitting an impulse from neuron to neuron. The energy released is considerable, and amplifies an even small initial stimulation for easier transmission.

IV. MEDICINAL ASPECTS OF ANESTHETICS

From the surgeon's point of view a classification of anesthetics can be obtained when their effect on the four stages of anesthesia is considered. The first two stages are called the induction period. In the first stage the anesthetic agent acts on the higher cortical center, while in the second stage the depressant action of the anesthetic is manifested on the higher motor center which releases the automatic lower mechanisms. After reaching the stage of analgesia and of "altered consciousness" the patient becomes unconscious in the second stage. In the third stage of anesthesia the spinal cord is affected. Sensation and spinal reflexes are abolished and the muscles relaxed. In the fourth stage of anesthesia, barely ever desirable in the operating room, the anesthetic paralyzes the vital functions of the medulla and of the brain stem. It may involve rapid respiratory failure and collapse of the vital motor functions and thereby lead to death.

Ether and chloroform go through the traditional stages of anesthesia very clearly. On the other hand, divinyl ether, ethylene and cyclopropane reach the third stage of analgesia very quickly and induction is quite rapid. Surgical anesthesia is obtained almost instantaneously by the intravenous injection of barbiturates which brings about unconsciousness within a few seconds. These characteristics of anesthetics determine to a large extent their usefulness in the clinic.

Another characteristic desirable of an anesthetic is an uneventful recovery from the anesthesia without untoward side effects such as nausea, mucous irritation and excitement. Post-anesthetic sleep may or may not be desirable depending upon the type of surgery performed.

If an ideal anesthetic could be obtained the patient would hope that it would cause rapid and pleasant induction without irritation, without unpleasant odor, and with a short recovery period free of discomfort. It goes without saying that such an anesthetic should not be explosive in mixtures with air. Almost all the inhalation anesthetics cause occasional

anesthesia accidents. It should have a wide margin of safety, a low toxicity, it should not be altered in the body, but excreted unchanged, and should have as few side effects as possible. It should also be sufficiently potent so that it can be administered with a high percentage of oxygen, and volatile enough to be exhaled immediately and excreted when the anesthetic mask is removed. In addition it should be inexpensive to manufacture, stored without chemical change and purified easily.

Of all known gaseous anesthetics nitrous oxide comes closest to being an ideal anesthetic but its relatively low activity does not place it in a class by itself.

1. Volatile Anesthetics

Methods of Administration

The so-called open method can be used only with those volatile anesthetics which, at room temperature at least, are liquids, that is, ether, divinyl ether, and chloroform. A mask consisting of several layers of gauze is placed over the patient's face and the anesthetic is dropped on the mask. The method is wasteful because much of the anesthetic is lost into the atmosphere. The concentration of the anesthetic is hard to control. By placing a towel over the mask, the so-called semi-open method makes a somewhat better use of the anesthetic.

In the closed method, the patient rebreathes the anesthetic mixture. This requires a special apparatus consisting of a mask fitting tightly over the face of the patient, a so-called rebreathing bag which contains absorbents for carbon dioxide and for moisture and has openings to introduce oxygen, carbon dioxide and the anesthetic. It has the chief advantage of allowing a close and economic control of the anesthetic. The heat of the exhaled air keeps the patient's face warm. The method permits a smoother induction and a careful control of the anesthetic stages. The chief disadvantage of this method is the dilution of the anesthetic mixture by nitrogen which has been dissolved in the patient's blood and is slowly liberated into the rebreathing bag; the bag has to be vented from time to time to prevent undue dilution of the anesthetic mixture.

2. Ether and Chloroform

An advantage of ether and chloroform over the permanent gaseous anesthetics is the possibility of using them in the open method by which a concentration of 6 to 8% of ether in the inspired air necessary to produce anesthesia may be reached. The concentration in the blood during surgical anesthesia may go up to 150 mg. per 100 cc. of blood.

Like nitrous oxide and cyclopropane, ethyl ether stops respiration before it stops the circulation if the patient should ever reach the fourth stage of anesthesia. Consequently, artificial respiration is often successful

in reviving the patient. This is the chief advantage of ether over chloroform which first stops circulation and *then* respiration, and thus makes resuscitation by artificial respiration virtually impossible. In addition, chloroform may cause extensive liver damage and has therefore been abandoned except in the tropics and in cases where its slightly lower volatility is of advantage.

Disadvantages of using ethyl ether are its enormous inflammability and its capacity of forming peroxides which can, however, be countered by very careful purification and stabilization. Chloroform is easily decomposed to phosgene by hot surfaces or flames; phosgene is toxic in concentration of 1:40,000 and has led to fatalities in the operating room.

3. Ethylene

Based on the observation that small amounts of ethylene can bleach pigmented flowers Luckhardt[6] studied the effects of this gas on higher animals. Ethylene was introduced as a clinical anesthetic later but it has never attained the same importance as ether. A high concentration (85–90%) of ethylene is required to produce anesthesia and in order to avoid hypoxia in the brain it must be administered with a considerable percentage of oxygen; this makes the anesthetic mixture highly explosive.

4. Divinyl Ether

Since ethylene anesthesia is characterized by a very short induction period, much shorter than that of ether, it occurred to Leake[7, 8] that a combination of the molecule of ethylene and of ether might lead to a useful anesthetic. Ruigh and Major[9] synthesized divinyl ether from ethylene-chlorohydrin via β-chloroethyl ether:

$$2\,CH_2ClCH_2OH \rightarrow (ClCH_2CH_2)_2O \xrightarrow{NaOC_2H_5} (CH_2{=}CH)_2O$$

The drug was found to live up to expectations. It has several distinct advantages over ethyl ether, a shorter duration of the induction period, quick and uneventful recovery, and the very small percentage (2%) of postoperative nausea as compared with an average of 57% for ether. The main disadvantage of divinyl ether is its very high volatility which does not permit its use in the open method, its tendency to undergo oxidation and polymerization which makes necessary stabilization with antioxidants such as 2-phenylaminonaphthalene, and the occasional occurrence of hepatic injury after its use.

[6] Luckhardt and Lewis, *J. Am. Med. Assoc.*, **81,** 1851 (1923).
[7] Leake and Chen, *Proc. Soc. Exptl. Biol. Med.*, **28,** 151 (1930).
[8] Leake, Knoefel, and Guedel, *J. Pharmacol. Exptl. Therap.*, **47,** 5 (1933).
[9] Ruigh and Major, *J. Am. Chem. Soc.*, **53,** 2662 (1931).

5. Other Volatile Anesthetics

As might be expected not only ethylene but a large number of other saturated and unsaturated hydrocarbons are potentially useful as anesthetics. Acetylene particularly has had a short-lived popularity but such gases as methane, ethane, propane, etc. have also been tried. The chlorinated derivatives of methane show a progressive increase of anesthetic activity as their halogen content rises. The first useful anesthetic is attained in chloroform while methyl and methylene chloride are not enough depressant. Carbon tetrachloride is more powerful than chloroform but also much more toxic.

In the series of chlorinated ethanes, ethyl chloride and trichloroethane have received particular attention. Ethyl chloride is still widely used as a general anesthetic for operations of short duration, and trichloroethylene has reached some popularity in the tropics because of its higher boiling point. The ease with which it reaches the stage of analgetic effect has been used for the relief of pain in migraine and angina pectoris.

6. Cyclopropane

Cyclopropane was introduced as an anesthetic in 1930 by Henderson and Luckhardt.[10] It is synthesized from 1,3-dibromopropane by the action of metals. A useful synthesis was accomplished when Haas[11] chlorinated propane from natural gas to 1,3-dichloropropane without simultaneous formation of the 1,2-isomer. This can then be cyclized to cyclopropane by the same procedure as 1,3-dibromopropane. The most potent of the anesthetic gases, cyclopropane can lead to complete analgesia without producing unconsciousness if inhaled at very low concentrations. In concentrations of 26% it produces surgical anesthesia, but this concentration can be cut into half if preanesthetic medication has been given, particularly atropine and scopolamine. In combination with Avertin (see below) cyclopropane approaches the ideal anesthetic from the surgeon's point of view. Its toxicity is low, its therapeutic index high, and it is rapidly absorbed and excreted by the lungs. Its main disadvantages are, as in the case of some of the other gaseous anesthetics, its explosiveness and inflammability when mixed with oxygen.

Krantz and his co-workers observed that cyclopropyl ethers, the methyl ether, Cyprome, the ethyl ether, Cypreth, and others may become useful as surgical anesthetics.[12]

[10] Henderson and Luckhardt, *Anesthesia & Analgesia*, **9,** 1 (1930).
[11] Haas, McBee, Hinds, and Gluesenkamp, *Ind. Eng. Chem.*, **28,** 1178 (1936).
[12] Krantz, Carr, Forman, and Evans, *J. Pharmacol. Exptl. Therap.*, **69,** 207 (1940).

7. Nitrous Oxide

In contrast to other anesthetic gases nitrous oxide is very soluble in water. Blood takes up 45 volume per cent. The compound does not combine with hemoglobin but is carried in solution to the central organs where it exerts its main effect. When administered in a 9:1 mixture with oxygen it is a safe anesthetic with very few side effects. The oldest known anesthetic, ("laughing gas"), it produces anesthesia in a relatively short time and recovery is rapid and usually without after-effects. It is now widely used to induce surgical anesthesia but is usually followed up with ether since mixtures of nitrous oxide and the necessary amount of oxygen do not give a sufficient degree of muscular relaxation for major surgical operations. If nitrous oxide is given without dilution with oxygen it is not satisfactory for operations lasting more than ninety seconds since it produces anoxia (complete lack of oxygen) in the nervous tissues.

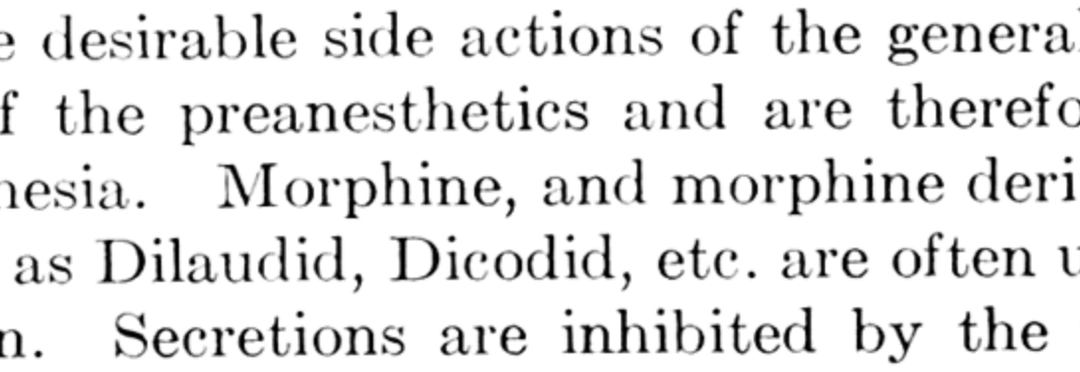
V. PREANESTHETIC MEDICATION

A number of drugs may be used to prepare a patient for surgical anesthesia with inhalation anesthetics. The purpose of these preanesthetic drugs is to relieve pain, to decrease apprehension, especially in highly nervous individuals and to reduce the stage of excitement of the induction period of anesthesia. Even more important is the synergism of certain compounds with inhalation anesthetics which lessens the amount of the latter for completion of surgical anesthesia. Several of the pharmacological properties which are desirable side actions of the general anesthetics are exhibited by some of the preanesthetics and are therefore useful in the preparation for anesthesia. Morphine, and morphine derivatives with improved properties such as Dilaudid, Dicodid, etc. are often used in small doses before an operation. Secretions are inhibited by the use of atropine, and thereby the incidents of post-operative pulmonary complications, nausea, etc. are lessened.

1. Scopolamine

Many anesthetists prefer scopolamine in combination with morphine to other preoperative preparations. Scopolamine (VII-1) is an alkaloid of *Scopolia* species from the family of solanaceous plants.[13] It not only

(VII-1)



[13] Willstätter and Berner, *Ber.*, **56,** 1079 (1923).

inhibits secretions but also acts as a depressant on the central nervous system, reducing excitement and producing twilight sleep accompanied by amnesia.

The preanesthetic use of barbiturates is restricted very largely to inducement of sleep and sedation in the preparation for surgery.

2. Avertin

Widely employed is tribromoethanol which is used in a solution in tertiary amyl alcohol (amylene hydrate) under the name of Avertin. The use of this drug was conceived from a consideration of the pharmacological mechanism of chloral. Chloral had long been known to be an excellent hypnotic; its hypnotic action is not due, as originally suspected, to a cleavage to chloroform in the alkaline fluids in the body but instead it undergoes reduction to trichloroethanol which then actually exerts the apparent hypnotic action of the parent aldehyde. It was only logical to test tribromoethanol as a depressant. A guiding thought in its preparation may have been the influence of the halogen atoms on the molecule of ethyl alcohol which in itself is not classifiable as a depressant under the lipid-water distribution theory. Introduction of the halogen atoms makes alcohols, aldehydes etc. more likely to exhibit centrally depressant effects.

Avertin causes patients to fall asleep after a short induction period. The drug is administered rectally and thus allays the apprehensions of an anesthetic mask and of presurgical manipulations. Since its anesthetic index is not too favorable, Avertin is mostly used as a basal anesthetic, that is, anesthesia is completed by small amounts of some of the volatile or gaseous inhalation anesthetics. Post-operative distress such as nausea is eased after Avertin narcosis. The chief disadvantage of Avertin anesthesia is the fact that it cannot be quickly removed from the organism if collapse threatens. The safety factor of removing the anesthetic mask present in inhalation anesthesia is obviously not available with a fixed non-volatile anesthetic.

In addition to its use in anesthesia, Avertin has been found to be of advantage as a preventive anticonvulsant. It is useful in cases of brain surgery because it lowers intracranial pressure, and in patients with pulmonary disease because it is not excreted by the lungs and synergistically reduces the amount of the inhalation anesthetic which might irritate the lungs. Should it be necessary to resuscitate a patient during Avertin narcosis, central stimulants such as Metrazol, caffeine, ephedrine, carbon dioxide, etc., may have to be used.

The synthesis of Avertin by Willstätter[14] consisted in a reduction of

[14] Willstätter and Duisberg, *Ber.*, **56,** 2283 (1923).

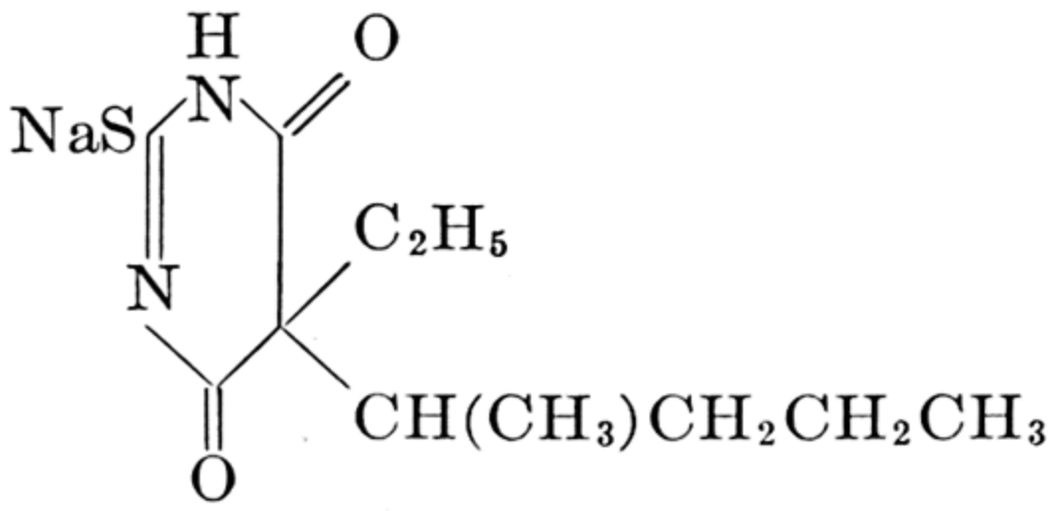
bromal with brewer's yeast. Since the more general acceptance of the Ponndorf-Meerwein-Verlay method in recent years, aluminum isopropoxide may be substituted advantageously for the older reducing agent.

$$Br_3CCHO \xrightarrow{Al(OC_3H_7)_3} Br_3CCH_2OH$$

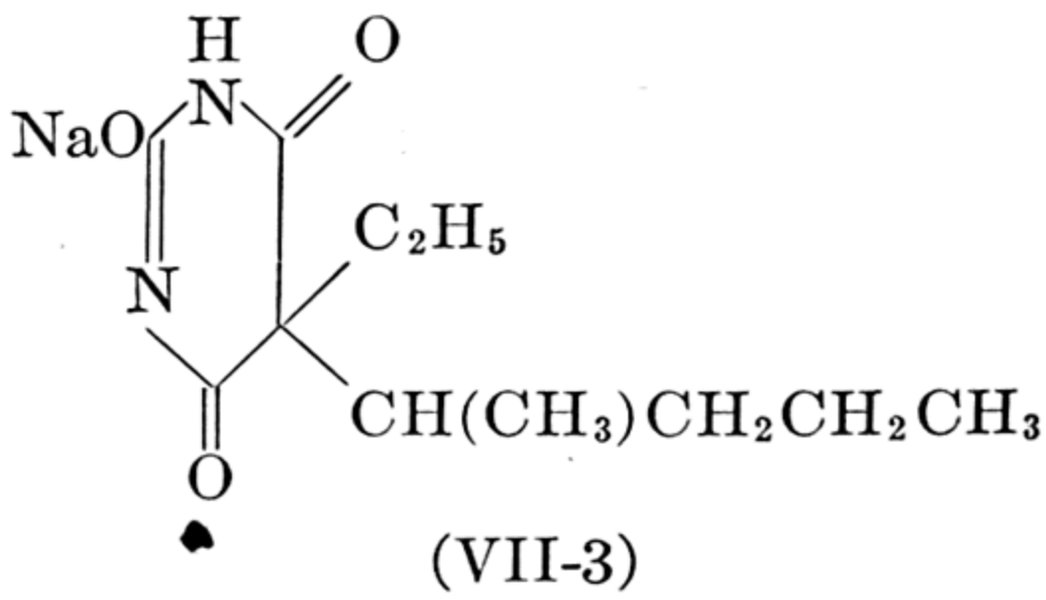
Relaxation of muscles during anesthesia is one of the most important prerequisites to successful surgery. In recent years, Myanesin and Glyketal (Chapter XXII) have been used as muscle relaxants as adjuncts to surgical anesthetics.

VI. BARBITURATES AS ANESTHETICS

Intravenous injection of some of the prompt acting thiobarbiturates produces surgical anesthesia of very short duration. The most widely used drug of this series is sodium 5-ethyl-5-isoamyl-2-thiobarbiturate (VII-2, Pentothal; pentothiobarbital sodium), the sulfur analog of Nembutal (pentobarbital sodium, VII-3).



(VII-2)



(VII-3)

VII. SPINAL ANESTHESIA

By injecting local anesthetics into the spinal fluid all types of nervous impulses centered in this region may be blocked. This procedure is useful in surgery of the lower abdomen, the rectum and the lower extremities.

The most widely used spinal anesthetics are Novocain and Pontocaine (Chapter VIII). The procedure of spinal anesthesia is not without drawbacks. Side-effects may include loss of motor tone, and a dangerous drop in blood pressure due to paralysis of the vasoconstrictor innervation. The advantages lie in the fact that the patient remains conscious and usually experiences relatively little post-operative distress.

CHAPTER VIII

Local Anesthetics

Drugs which may be applied locally and there block afferent nervous conduction from the periphery of the nerve path are called local anesthetics. If the site of their application is near a peripheral nerve ending, they prevent nervous reactions in this specific area. On the other hand, if applied to a central nervous organ they block the transmission of impulses only from the portion of the central organ involved, or of stimuli received by it. Thus, definite local regions may be anesthetized without affecting other parts of the nervous system. This property distinguishes the local anesthetics from general anesthetics.

I. THEORIES OF ACTION

The theories of cell penetration which have proved fruitful in the discussion of general anesthetics hold also for the explanation of the preferential penetration of lipid nervous tissues by local anesthetics. As in the case of central anesthetics, these theories do not explain the mechanism of local anesthetic action. The few observations which clarify the latter can be summarized as follows.

Local anesthetics must be applied, as do all other drugs, in doses large enough to produce their effect. Increases of the effective doses do not cause general anesthesia but only systemic poisoning as the toxic level is reached. Smaller nerve fibers which offer a relatively large surface to chemical penetration with respect to their total volume, are more readily anesthetized than larger more compact fibers.

The effectiveness of a local anesthetic is measured not only by the degree of insensibility of the anesthetized area but also by the duration of its action. Most local anesthetics are absorbed fairly rapidly and must be administered therefore with a vasoconstrictor agent which will decrease the rate of absorption and thus keep them active at the site of application. Low concentrations of epinephrine are often used for this purpose. Incorporation of epinephrine has the added advantage of preventing premature destruction of the drug in the liver where the local anesthetics are detoxicated.

It will be seen in the following discussion that the majority of local anesthetics are basic compounds. They are handled in the form of their

salts, most commonly in the form of their soluble hydrochlorides or sulfates. The tissue fluids probably liberate from these salts the free bases, and administration of the free bases has been undertaken in several instances. In general, the free bases anesthetize tissues more effectively than the corresponding quantities of the salt. However, the free bases are frequently oily and easily oxidizable, and the stable salts of the local anesthetics are used generally for the sake of greater safety and ease of application.

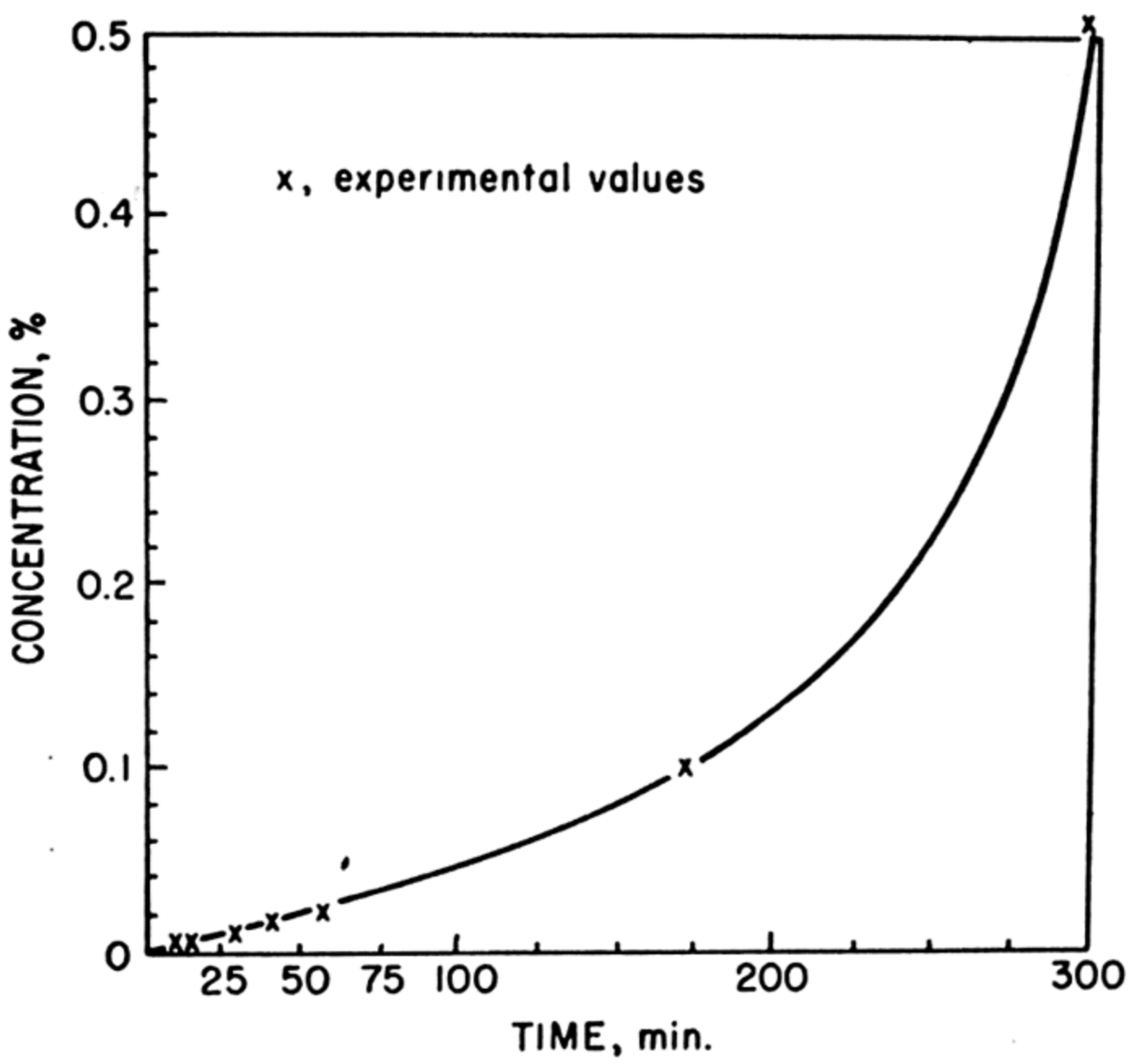


Figure 1. Relation of the Concentration of Nupercaine to the Duration of Its Action as Calculated by the Chain Formula[2]

The greater potency of the bases as compared with the salts suggested to Krahl, Keltch and Clowes[1] an investigation of the activity of undissociated molecules of the base on isolated cells. They studied the effect of sixteen different local anesthetics on the fertilized eggs and larvae of the sea urchin (*Arbacia punctata*) and determined simultaneously the dissociation constants of the drugs. The concentration of undissociated molecules outside the cell which is required to produce a 50% reduction in the rate of cell division of the *Arbacia* eggs, or the movement of the larvae, is independent of the pH of the medium provided the pH inside the cell is held constant. This seems to indicate that the basic local anesthetics penetrate the living cell entirely in the form of undissociated molecules. When the same experiment was performed and carbon dioxide was passed into the

[1] **Krahl, Keltch and Clowes,** *J. Pharmacol. Exptl. Therap.*, **68,** 330 (1940).

solution, the concentration of the anesthetic ion inside the cell was increased until an equilibrium with the undissociated molecules outside the cell was established. The local anesthetic activity of the compounds increased accordingly. Thus, the local anesthetic cations and not the undissociated molecules cause the anesthetic effect inside the cell. If ammonium hydroxide is added instead of carbon dioxide the local anesthetic cation concentration inside the cell decreases until equilibrium with the undissociated molecules outside the cell is established. The activity of the compounds was found to decrease in the same ratio.

A similar relation between the penetration of bacterial cells by not ionized molecules, and the bacteriostatic activity of the anions exists in the group of sulfa drugs (Chapter XXXIV). In this light, the preceding discussion may be regarded as a variant of the Meyer-Overton theory expressing solubilities and cell-affinities in terms of the ionization theory.

The relation of the concentration of the local anesthetic to its duration has been studied in the case of Nupercaine.[2] A so-called chain formula corresponds best to the experimentally obtained values.

$$y = \frac{m}{2}\left[a_1{}^{x+p} + a_2{}^{(-x+p)}\right] - k$$

In this equation x is the duration of anesthesia, y is the dosage used, and m, a, and k are constants.

II. TESTS AND METHODS OF APPLICATION

The testing of local anesthetic activity in animals is carried out most often by "topical" (surface, terminal) application to the surface of the rabbit cornea. The cornea is touched with a needle after anesthesia has taken place, and the concentration of the solution of the drug which produces local insensibility is taken as a measure of the activity of the compound. This testing method also provides a clue to the most common side effect of otherwise useful drugs, that is, local irritation of tissue.

Introduction of a sciatic nerve sensory block in the frog permits another good evaluation of small amounts of a drug. After determination of the systemic toxicity, intercutaneous injection into humans may sometimes serve as a testing method using the wheal in the skin resulting from this procedure as a measure of activity.

On the clinical level, local anesthetics are often applied by infiltration anesthesia. The drug is injected into the lower layers of the skin, either directly at the site of surgery, or in a so-called ring block in a circular area around the field of operation.

[2] Miescher, *Helv. Chim. Acta*, **15**, 189 (1932).

Acute toxic symptoms encountered in man are counteracted best by hypnotics, especially by barbiturates since these drugs arrest the convulsions resulting from an overdose of the anesthetic. They may even be given prophylactically, and the minimum lethal dose of the local anesthetic may be stepped up three to four times by this procedure.

In block or conduction anesthesia, the transmission of impulses in the nerve truck supplying the area to be anesthetized is interrupted. Spinal anesthesia is one form of this procedure. Another clinical modification of this technique is epidural anesthesia in which the drug is injected into the epidural space and produces anesthesia of upper portions of the body.

III. COCAINE

The development of local anesthesia did not hit its stride until the discovery of the local anesthetic properties of cocaine. This coca alkaloid had been known to have a numbing effect since the time of early Spanish colonization in South America, but its activity was first established by Köller who tested its effect on the rabbit cornea. The alkaloid not only exerts a strong local anesthetic action but also has the advantage of producing vasoconstriction and thus retaining the drug at the site of application. Properties which detract from the medicinal value of cocaine are its high toxicity, its addiction liability and cortical stimulation. Because of the latter manifestation cocaine had been used as a hallucinant and euphoric during the middle ages.

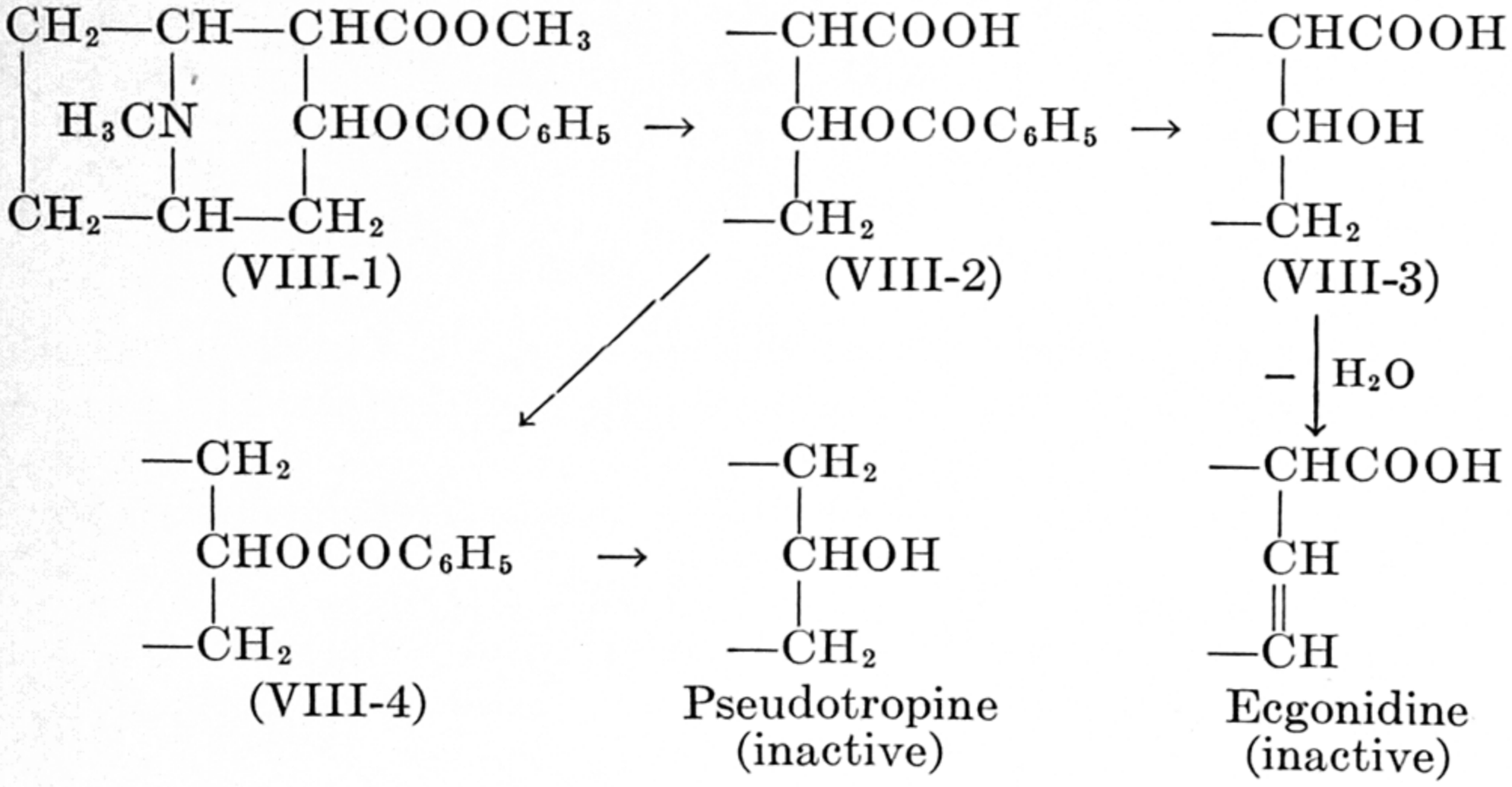
These properties together with the relatively high price of cocaine, the danger of its administration and the legal restrictions imposed on the drug on account of its addiction liability have led to an intensive search for a non-habit forming, less toxic and possibly more potent and longer-lasting local anesthetic. In spite of the fact that this search has produced literally hundreds of compounds with local anesthetic activity of which many could be used in the clinic, cocaine has not lost its place in therapy altogether. It is still used widely in ophthalmology because of its mydriatic action on the eye.

1. Variations of Structure

(a) Tropane Derivatives

The derivation of the most important group of local anesthetics, the dialkylaminoalkyl esters of aromatic and similar acids, presents a standard example of medicinal-chemical thought. Based on the structural model of cocaine (VIII-1) a number of experiments were carried out to determine which of the portions of its molecule are responsible for its local anesthetic action. During the study of close structural analogs as well as the di-

astereoisomers of cocaine it was found that either the hydrolysis of the carbomethoxy (VIII-2) or the benzoate group led to inactive compounds (ecgonine, VIII-3), but the restoration of the benzoate group in the decarbomethoxylated cocaine (tropacocaine, VIII-4) produced again a local anesthetic. The importance of the tertiary nitrogen atom seemed to be less clearly definable.



In order to prove the significance of the tropane ring system for the local anesthetic effects of cocaine, several simple derivatives of piperidine containing only the six-membered ring of the condensed tropane system have been tested. Of special interest are α- and β-eucaine which contain peripheral alkyl groups simulating the cut-away pyrrolidine portion of tropane.

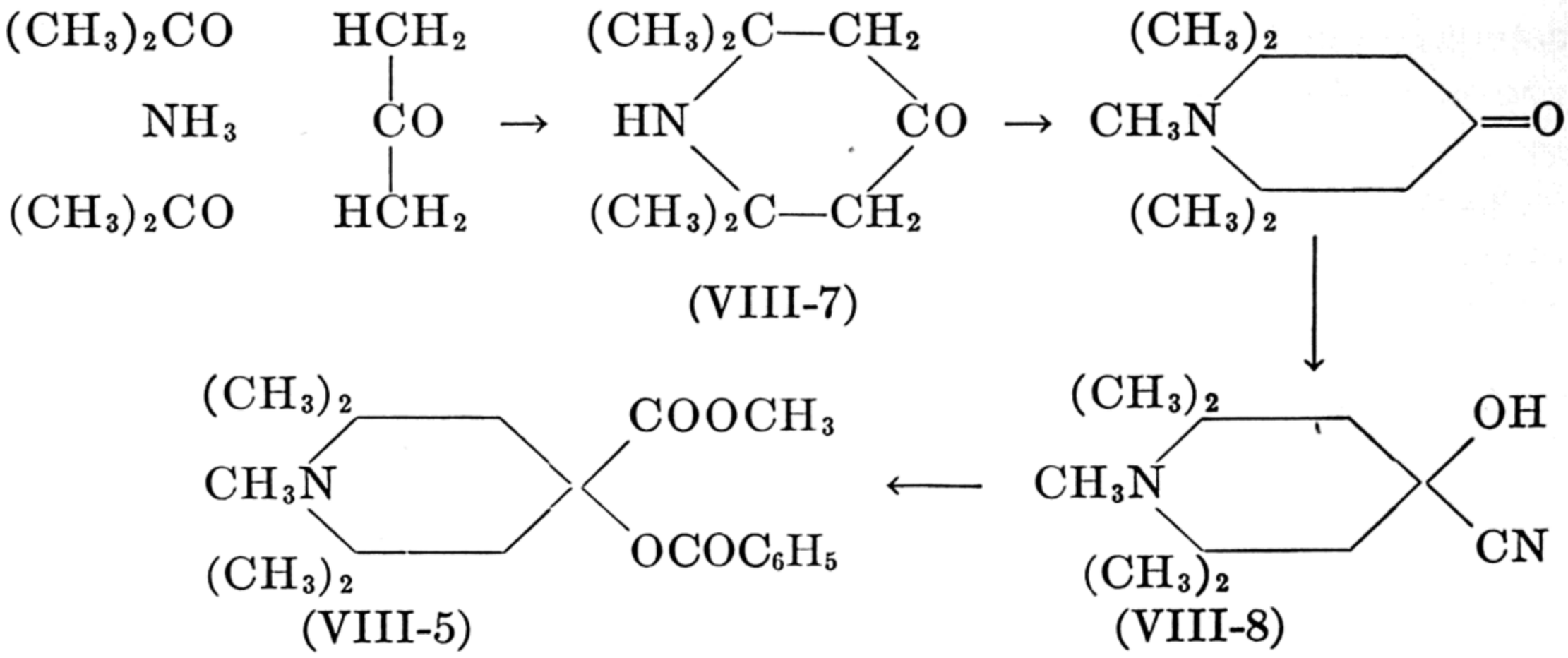
(b) The Eucaines

α-Eucaine (VIII-5) was prepared by condensation of acetone with ammonia to triacetonamine (VIII-7) the N-methyl derivative of which was converted to the cyanohydrin (VIII-8). O-Benzoylation and alcoholysis of the nitrile group to carbomethoxyl completed the synthesis.[3]

This compound was soon superseded by the less toxic β-eucaine (VIII-6) because of painful irritation at the site of injection. β-Eucaine was synthesized from diacetonamine (VIII-9) and acetaldehyde with subsequent reduction and benzoylation of the resulting derivative of γ-piperidone (VIII-10).

Both the optically active forms of the eucaines and the racemic mixtures exhibit about the same degree of local anesthetic activity. These experiments are adequate evidence for the fact that the tropane ring

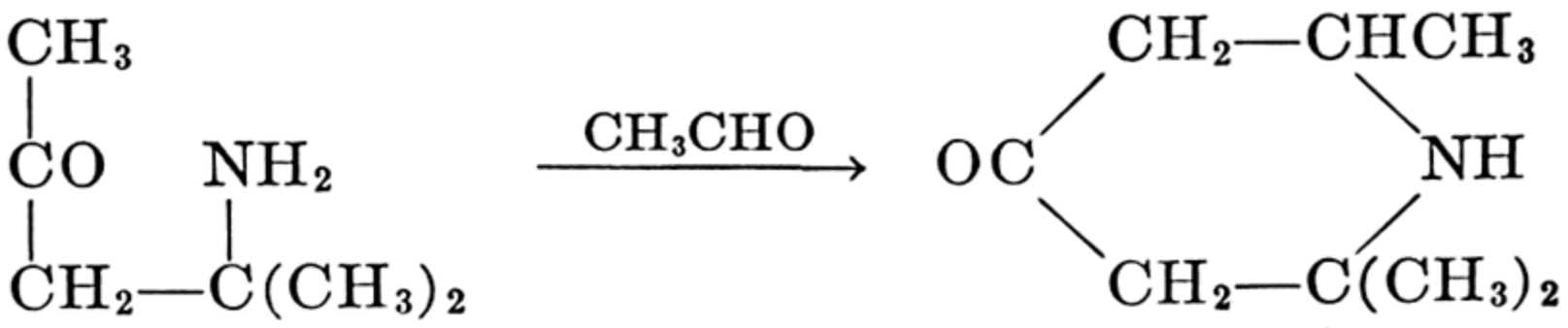
[3] Harries, *Ann.*, **296,** 328 (1897); **299,** 346 (1897).



(VIII-7)

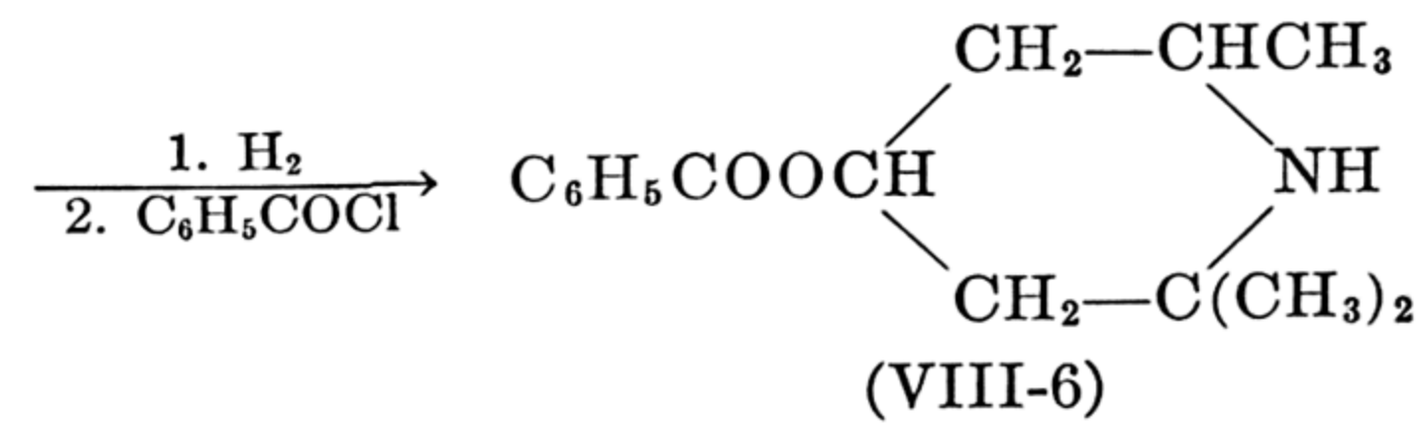
(VIII-5)

(VIII-8)



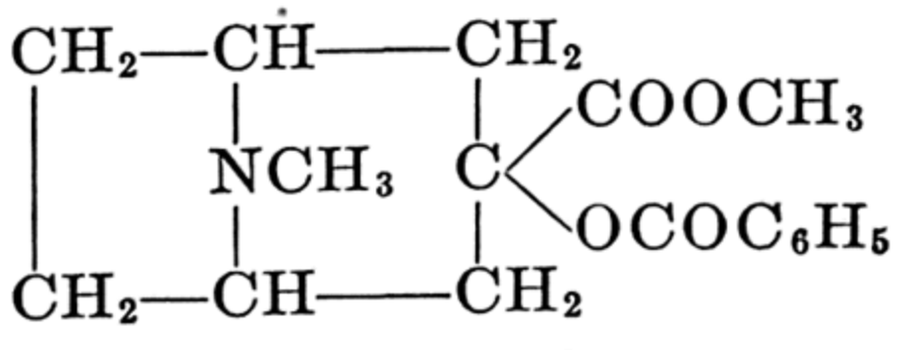
(VIII-9)

(VIII-10)



(VIII-6)

system is not needed for this particular activity. Strangely enough, α-cocaine (VIII-11) which resembles α-eucaine in the relative positions of its functional groups, is inactive.



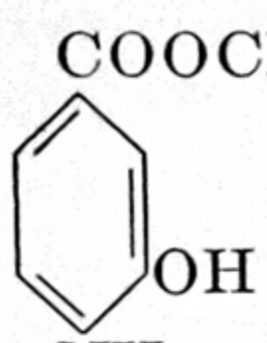
(VIII-11)

IV. BENZOCAINE

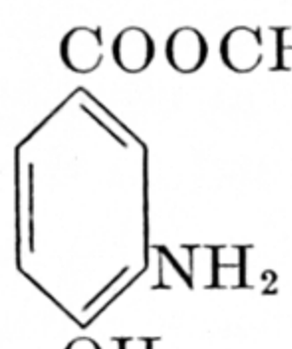
While this line of thought was followed at the turn of the century, another lead to local anesthetics centering around ethyl *p*-aminobenzoate

[4] Ritsert, as quoted by Bodendorf, *Deut. Apoth. Ztg.*, **49**, 1642 (1943).

was taken up by Einhorn. It was based on the discovery of Ritsert[4] who had introduced ethyl *p*-aminobenzoate as the *p*-phenylsulfonate under the name of subcutin into therapy. Modifications of the molecule of ethyl *p*-aminobenzoate soon led Einhorn to the compounds, Orthoform (VIII-12) and Orthoform New (VIII-13), the latter being prepared because of

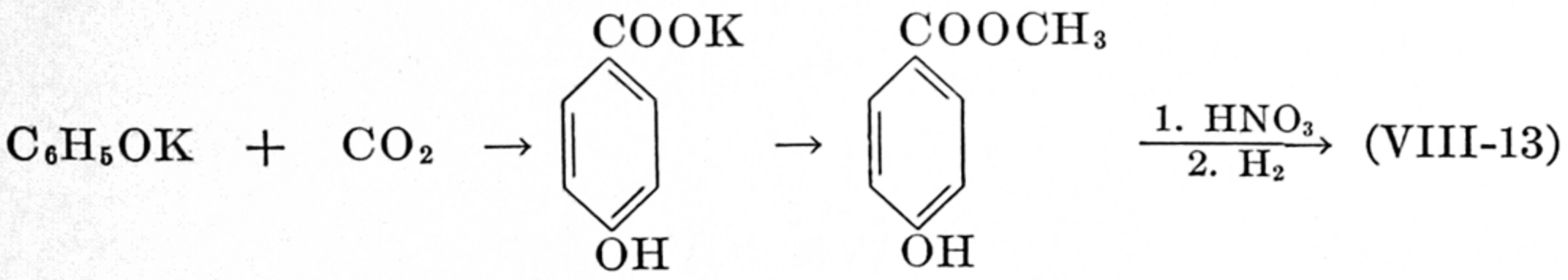


(VIII-12)



(VIII-13)

synthetic difficulties in the large scale production of Orthoform. Orthoform New is obtained by a Kolbe reaction with potassium phenolate which directs the entering carboxyl group into the *p*-position. Further steps include esterification, nitration, and reduction.



The successful application of similar esters as local anesthetics led Einhorn to stipulate that activity could be expected of any ester of an aromatic acid containing perhaps, but not necessarily, a basic group. His prediction has been borne out only to a certain extent since local anesthetic activity has been discovered in many types of organic chemicals.

Ethyl *p*-aminobenzoate (p-$H_2NC_6H_4CO_2C_2H_5$) has been retained in medicine under the names of benzocaine or Anesthesin. The corresponding butyl ester (p-$H_2NC_6H_4COOC_4H_9$) is known as Butesine and is used in the form of its picrate for the relief of pain on denuded surfaces, such as burns where the coagulating and antiseptic properties of picric acid are to be combined with the local anesthetic effect of the basic ester.

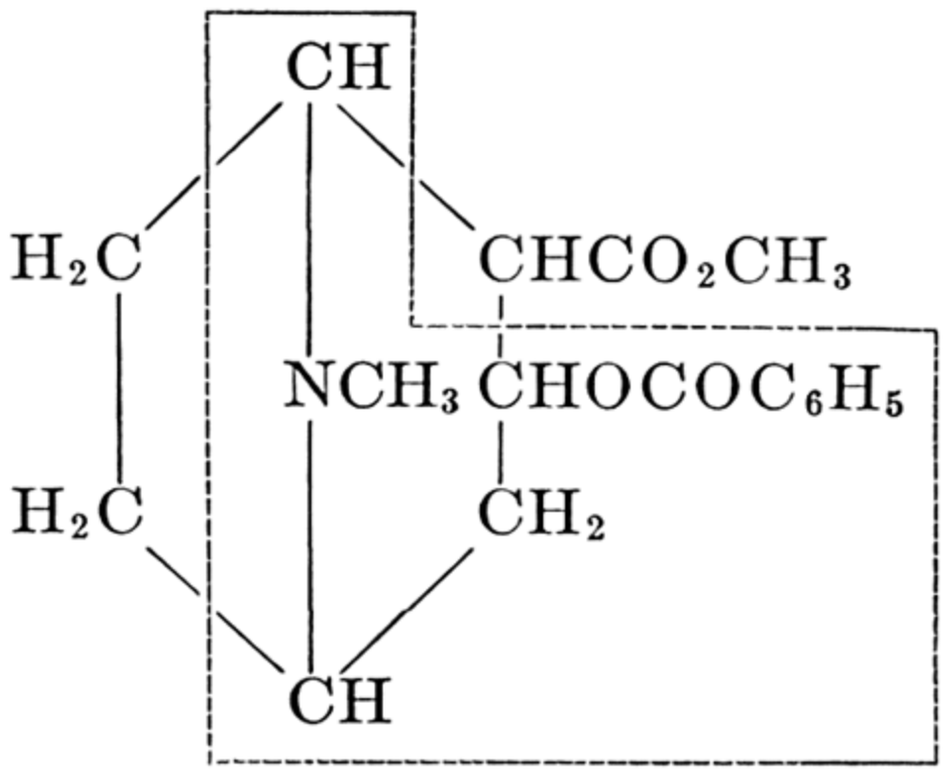
It is not surprising that the success of these simple aromatic compounds has led to extensive structural variations. In general, alkyl *p*-aminobenzoates show increased activity with a lengthening of the alkyl chain.[5] These compounds are relatively insoluble in water and exert a long-lasting surface effect.

[5] Adams, Rideal, Burnett, Jenkins, and Dreger, *J. Am. Chem. Soc.*, **48,** 1758 (1926).

V. PROCAINE

1. Derivation and Synthesis

The combined knowledge obtained from the degradation of cocaine, and the activity of the alkyl *p*-aminobenzoates, enabled Einhorn to proceed to the effective series of local anesthetic dialkylaminoalkyl esters of aromatic acids. If the idea of a certain group producing a certain action in a molecule is adhered to then the anesthesiophore group in the cocaine molecule (VIII-14) may be regarded as consisting of an aromatic acid esterified with a tertiary amino alcohol. By combination of this group



$= \quad R_2N—(CH_2)_n—OCOAr$

(VIII-14)

with that present in the alkyl *p*-amino-benzoates a series of compounds was prepared of which procaine (VIII-17) had the most favorable therapeutic ratio. Its monohydrochloride was called Novocain.[6] Its low toxicity together with its great effectiveness in injection anesthesia has made this compound the most widely accepted local anesthetic, and although many other similar compounds with better and more widely useful properties have been prepared the medical profession has preferred this compound for almost fifty years.

Drawbacks of procaine are, for instance, its low penetrating power which lessens its usefulness in the application to mucous membranes. The absence of any vasoconstrictor effect necessitates its use together with a vasoconstrictor agent such as epinephrine. On the positive side are the low cost of its manufacture, the ease of its synthesis and stability of its solutions.

Procaine is manufactured from *p*-nitrobenzoic acid (VIII-16) which is obtained by oxidation of *p*-nitrotoluene (VIII-15). The routes leading to procaine (VIII-17) are outlined in Figure 2.

[6] Einhorn and Uhlfelder, *Ann.*, **371,** 131 (1909).

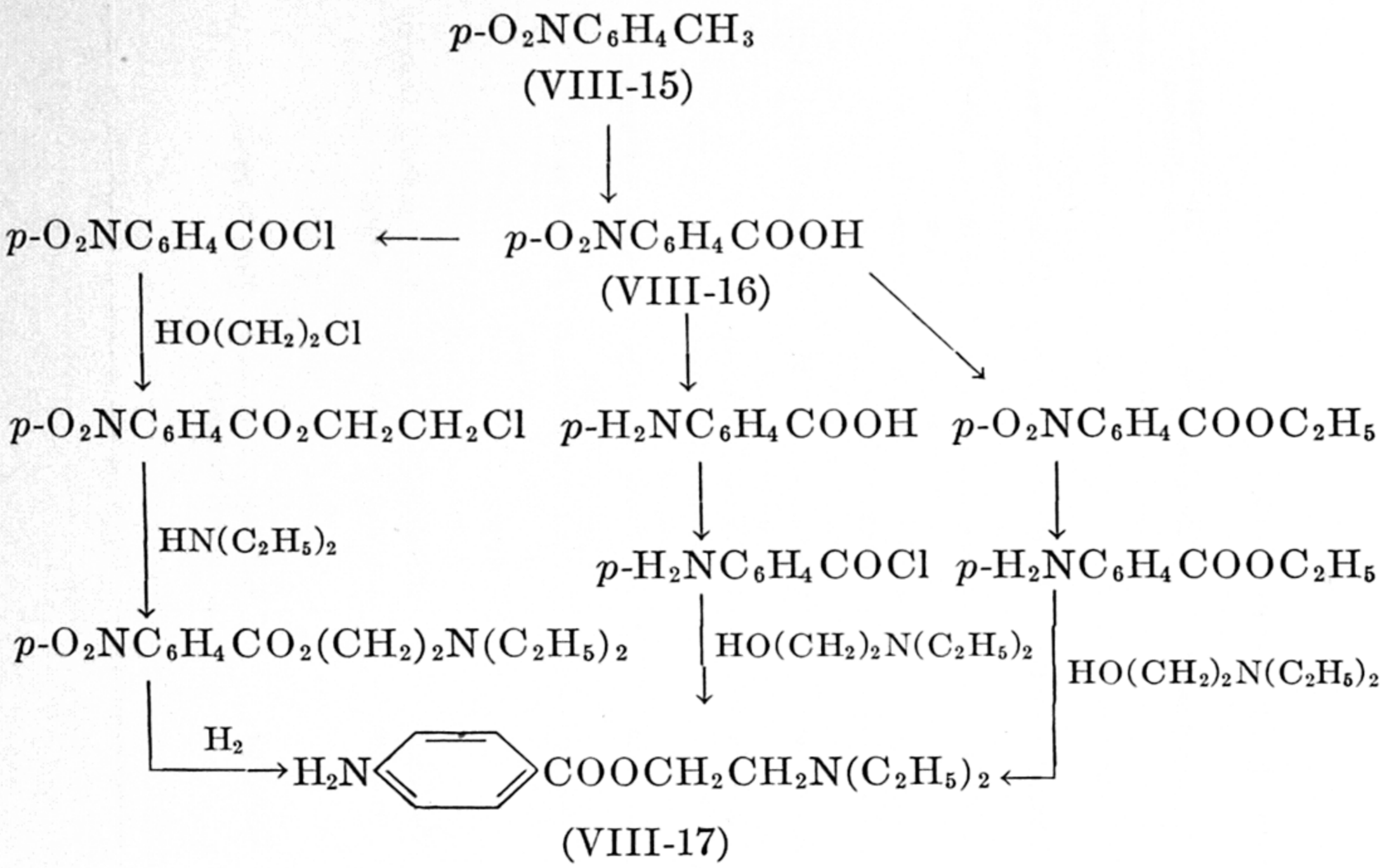


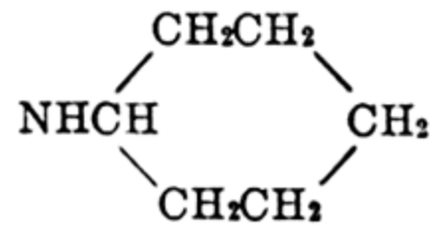
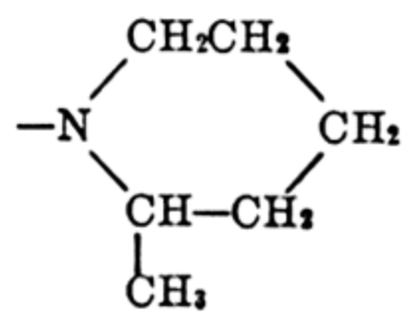
Figure 2. Syntheses of Procaine

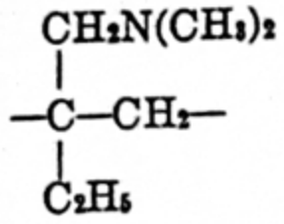
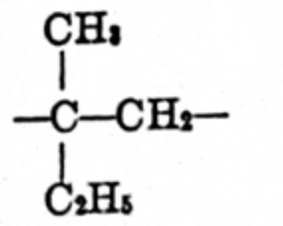
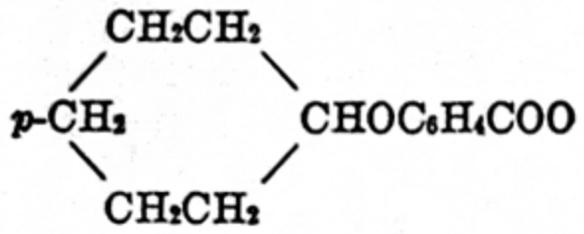
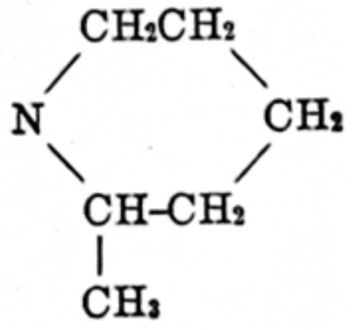
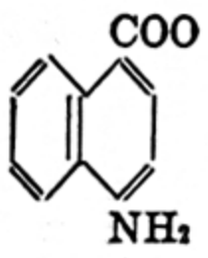
2. Structural Variations

Hope to improve the shortcomings of procaine and thereby to enrich the field of local anesthetics, has led to scores of structural variations. It is difficult to evaluate in all respects the improvement some of these drugs are said to offer because of the differences in pharmacological testing methods employed by various groups of workers. However, the fundamental structure of an aromatic acid with or without a nuclear substituent, and with the acid group esterified with a basic amino alcohol of simple or complex structure has remained the leading thought in the synthesis of many new local anesthetics.

A glance at the structure of such drugs (Table I) shows that synthetic difficulties could be expected mostly in the amino alcohol chain and not so much in the aromatic acid group. Benzoic acid, and variously substituted benzoic acids, particularly aminohydroxy and aminoalkoxy benzoic acids, have been used and are readily synthesized. Substitution of the carboxyl group by COSH has also received attention and anesthetic activity has been found in almost all dialkylaminoalkyl esters of these acids.

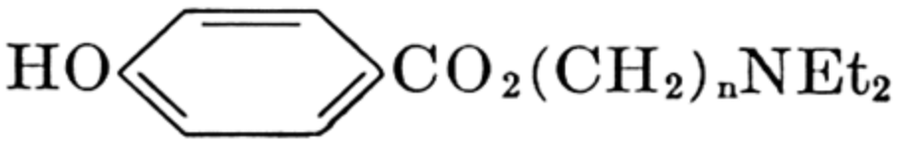
TABLE I. SOME LOCAL ANESTHETICS OF THE BASIC ESTER TYPE

RCOO—	—$(CR_2)_n$—	—NR_2	Common names	Chemical name	Typical modes of application
p-$H_2NC_6H_4COO$	—$(CH_2)_2$—	$N(C_2H_5)_2$	Procaine, Novocain	2-Diethylaminoethyl *p*-aminobenzoate	Most methods, spinal, not topical
p-$H_2NC_6H_4COO$	—$(CH_2)_3$—	$N(n\text{-}C_4H_9)_2$	Butacaine, Butyn	3-*n*-Butylaminopropyl *p*-aminobenzoate	Topical, eye, causes no mydriasis
p-$H_2NC_6H_4COO$	—$CH_2C(CH_3)_2CH_2$—	$N(C_2H_5)_2$	Larocaine	Diethylaminoneopentyl *p*-aminobenzoate	Infiltration, long duration
p-$H_2NC_6H_4COO$	(—$CHCH_3)_2CH_2$—	$N(CH_3)_2$	Tutocaine, Butamine	α,β-Dimethyl-γ-dimethylaminopropyl *p*-aminobenzoate	Corneal, infiltration
p-$H_2NC_6H_4COO$	—$(CH_2)_2$—	$NH\text{-}n\text{-}C_5H_{11}$	Amylcaine	2-*n*-Amylaminoethyl *p*-aminobenzoate	Most methods, topical
p-$H_2NC_6H_4COO$	—$CH_2CHCH_2CH(CH_3)_2$ (with —CH_3 branch)	$N(C_2H_5)_2$	Panthesin	2-[iso-Butyl]-2-diethylaminoethyl *p*-aminobenzoate	
p-$H_2NC_6H_4COO$	—$(CH_2)_2$—	$NHCH_2CH(CH_3)_2$	Monocaine	2-Isobutylaminoethyl *p*-aminobenzoate	Topical, infiltration
p-$(n\text{-}C_4H_9NH)C_6H_4COO$	—$(CH_2)_2$—	$N(CH_3)_2$	Pontocaine, Tetracaine	Dimethylaminomethyl *p*-*n*-butylaminobenzoate	Topical, spinal
C_6H_5COO	—$CH(CH_3)CH_2$—		Hexylcaine, Cyclaine	1-Cyclohexylamino-2-propyl benzoate	Most methods (low activity)
C_6H_5COO	—$(CH_2)_3$—		Metycaine	3-(2-Methylpiperidino) propyl benzoate	Most methods

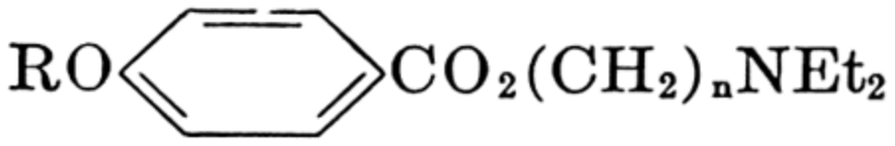
RCOO—	—$(CR_2)_n$—	—NR_2	Common names	Chemical name	Typical modes of application
C_6H_5COO		$N(CH_3)_2$	Alypin	1-Dimethylamino-2-dimethylaminomethyl-2-benzoxybutane	Most methods, mydriatic
C_6H_5COO		$N(CH_3)_2$	Stovain	2-Dimethylamino-1-methyl-1-ethyl-ethyl benzoate	
p-$C_2H_5OC_6H_4COO$	$—(CH_2)_2—$	$N(C_2H_5)_2$	Diethoxin	Diethylaminoethyl *p*-ethoxybenzoate	
	$—(CH_2)_3—$		Surfacaine, Cyclomethylcaine	3-(2-Methylpiperidino)-propyl *p*-cyclohexyloxybenzoate	Most methods
p-$CH_3OCH_2CH_2NHC_6H_4COO$	$—(CH_2)_2—$	NHC_5H_{11}	Dolantin	Amylaminoethyl *p*-methoxyethylamino benzoate	Most methods
$C_6H_5CH{=}CHCOO$	$—(CH_2)_3—$	$N(C_2H_5)_2$	Apothesin	3-Diethylaminopropyl cinnamate	Infiltration, spinal
p-$H_2NC_6H_4COS$	$—(CH_2)_2—$	$N(C_2H_5)_2$	Thiocaine	Diethylaminoethyl *p*-aminothiobenzoate	4–6× activity of procaine, 0.5× toxicity of cocaine
	$—(CH_2)_2—$	$N(C_2H_5)_2$	Naphthocaine	Diethylaminoethyl 4-amino-1-naphthoate	Infiltration

(a) Changes in the Ring

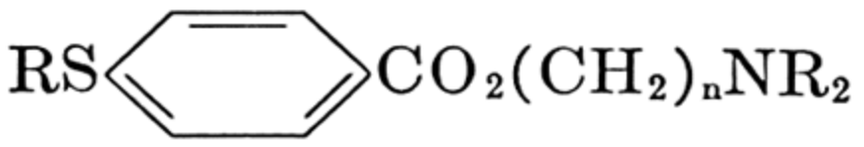
Substitution of the benzene ring by every possible atom or group has permitted the elaboration of certain generalizations. Just as the basic esters of *p*-aminobenzoic acid are, at least often, more potent than the analogous esters of benzoic acid, an increase of the size of the alkyl group in *p*-alkoxybenzoates (VIII-18) leads to a general rise in activity as compared with the corresponding *p*-hydroxybenzoates.[7–14] Thioether[15, 16]



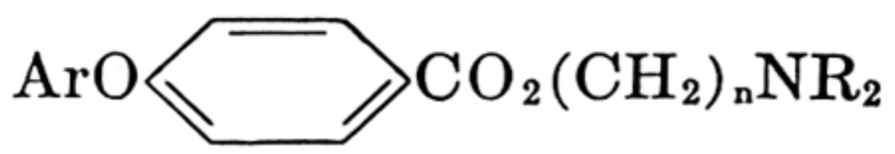
(VIII-18)



(VIII-19)



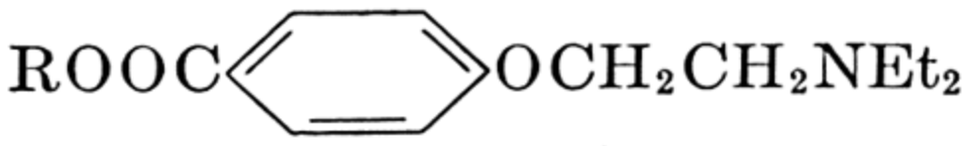
(VIII-20)



(VIII-21)

(VIII-20) and aryl ether groups[17] (VIII-21) may replace the nuclear alkoxyls without definite trends in effect.

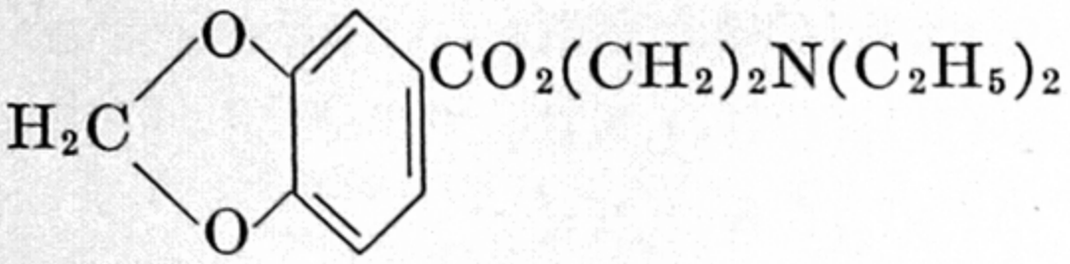
Variations of the nuclear ether groups have led to further aminoalkylbenzoates.[18] An interesting comparison has been drawn between dialkylaminoalkyl *p*-alkoxybenzoates (VIII-19) and the isomeric alkyl *p*-dialkylaminoalkoxybenzoates (VIII-22). The isomers with the basic group in the ester chain are more effective than those having basic nuclear ether functions.[19]



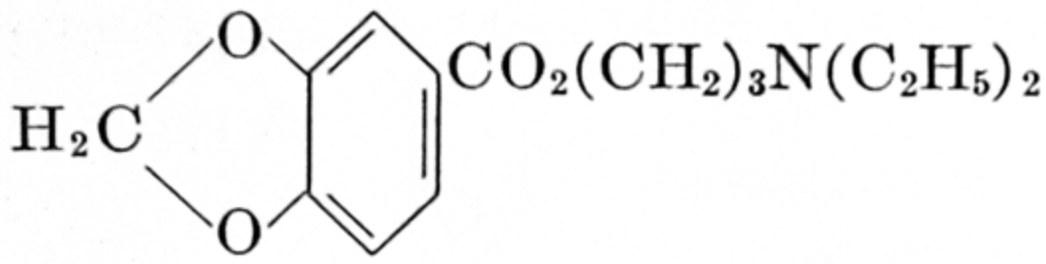
(VIII-22)

Cyclic nuclear ether groups are encountered in Piperocaine (VIII-23) and the homologous Piperothesine[20] (VIII-24).

[7] Fourneau and Matti, *J. Pharm. chim.*, **18,** 247 (1933).
[8] Rohmann and Scheurle, *Arch. Pharm.*, **274,** 110 (1936).
[9] McIntyre and Sievers, *J. Pharmacol. Exptl. Therap.*, **61,** 107 (1937); **63,** 34, 369 (1938).
[10] Christiansen and Harris, U. S. Pat. 2,243,694 (1941). Christiansen and Chase, U. S. Pat. 2,444,395 (1948).
[11] Vliet and Moore, U.S. Pat. 2,288,334 (1942).
[12] Rohmann, U. S. Pat. 2,081,712 (1937).
[13] Rovenstine and Cullen, *Anesthesia & Analgesia*, **18,** 86 (1939).
[14] Rohmann and Wilm, *Arch. Pharm.*, **280,** 76 (1942).
[15] Donleavy and English, *J. Am. Chem. Soc.*, **62,** 220 (1940).
[16] Hulpieu, Kitchel and Weatherby, *J. Pharmacol. Exptl. Therap.*, **68,** 395 (1940).
[17] Suter and Oberg, *J. Am. Chem. Soc.*, **53,** 1566 (1931).
[18] Blicke and Lilienfeld, *ibid.*, **65,** 2281 (1943).
[19] Rohmann and Koch, *Arch. Pharm.*, **276,** 154, 189 (1938).
[20] Kuwahata, Ochiai and Nukita, *Folia Pharmacol. Japon.*, **7,** 11, 409 (1928); *Chem. Abstr.*, **23,** 2499, 5236 (1929).



(VIII-23)

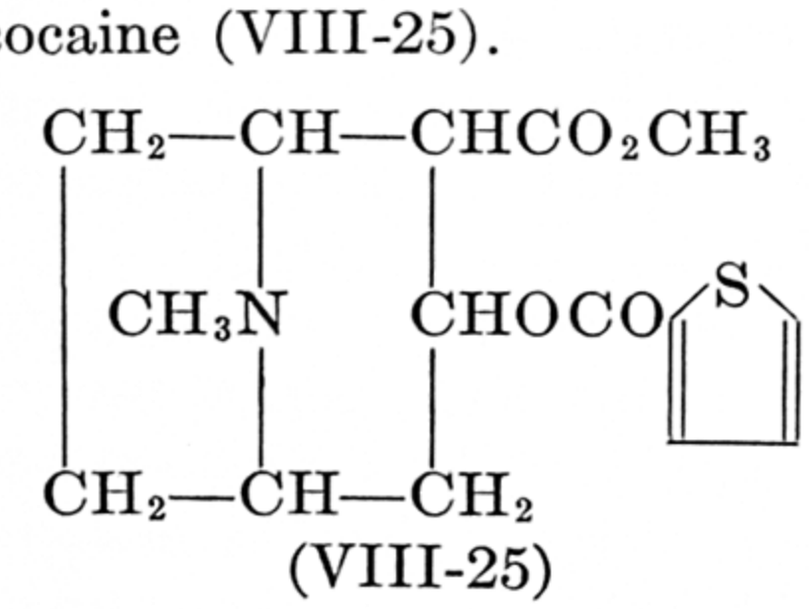


(VIII-24)

Anesthetic properties are also exhibited by similar esters derived from carboxylic acids in which the acid group is not attached directly to the nucleus. The stems of such compounds may be phenylacetic acid ($C_6H_5CH_2COOH$), α-phenylpropionic acid ($C_6H_5CH(CH_3)COOH$), cinnamic acid ($C_6H_5CH{=}CHCOOH$), 3,4-methylenedioxycinnamic acid, etc.

Basic esters of naphthoic[21-24], anthracenecarboxylic[25] and biphenylcarboxylic acids[26] possess local anesthetic properties, and the effect of substitution of these carbocyclic ring systems by amino, alkoxyl and other groups follows largely the pattern laid down in the benzene series.

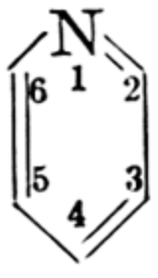
An almost innumerable variety of basic esters of heterocyclic carboxylic acids has been prepared and tested for local anesthetic activity.[27] They range from esters of furan, thiophene, pyrrole, pyridine, thiazole, quinoline, carbazole, dibenzofuran and dibenzothiophene carboxylic acids with simple dialkylaminoalkyl groups to such complex compounds as the 2-thenoyl isostere of cocaine (VIII-25).



(VIII-25)

The activity in a given heterocyclic system depends considerably on the nuclear position of the carboxyl group. Introduction of a second ring substituent such as amino or alkoxyl sometimes increases local anesthetic activity, for instance, in the series of dialkylaminoalkyl picolinates (VIII-26), nicotinates (VIII-27) and isonicotinates (VIII-28) which show surprisingly little activity. The thiazole analog of procaine is also inactive.[28]

[21] Fisk and Underhill, *J. Pharmacol. Exptl. Therap.*, **49,** 329 (1933).
[22] Blicke and Parke, *J. Am. Chem. Soc.*, **61,** 1200 (1939).
[23] Haury, Gruber and Drake, *J. Pharmacol. Exptl. Therap.*, **70,** 315 (1940).
[24] Rowe, *J. Am. Pharm. Assoc.*, **29,** 241 (1940).
[25] Lehmann and Knoefel, *J. Pharmacol. Exptl. Therap.*, **74,** 274 (1942).
[26] Christiansen, Harvey, Jones, and Braker, U. S. Pats. 1,976,921-4 (1934); 1,976,940 (1934).
[27] For references see Moore, *J. Am. Pharm. Assoc.*, **33,** 193 (1944).
[28] Dann, *Ber.*, **76,** 419 (1943).



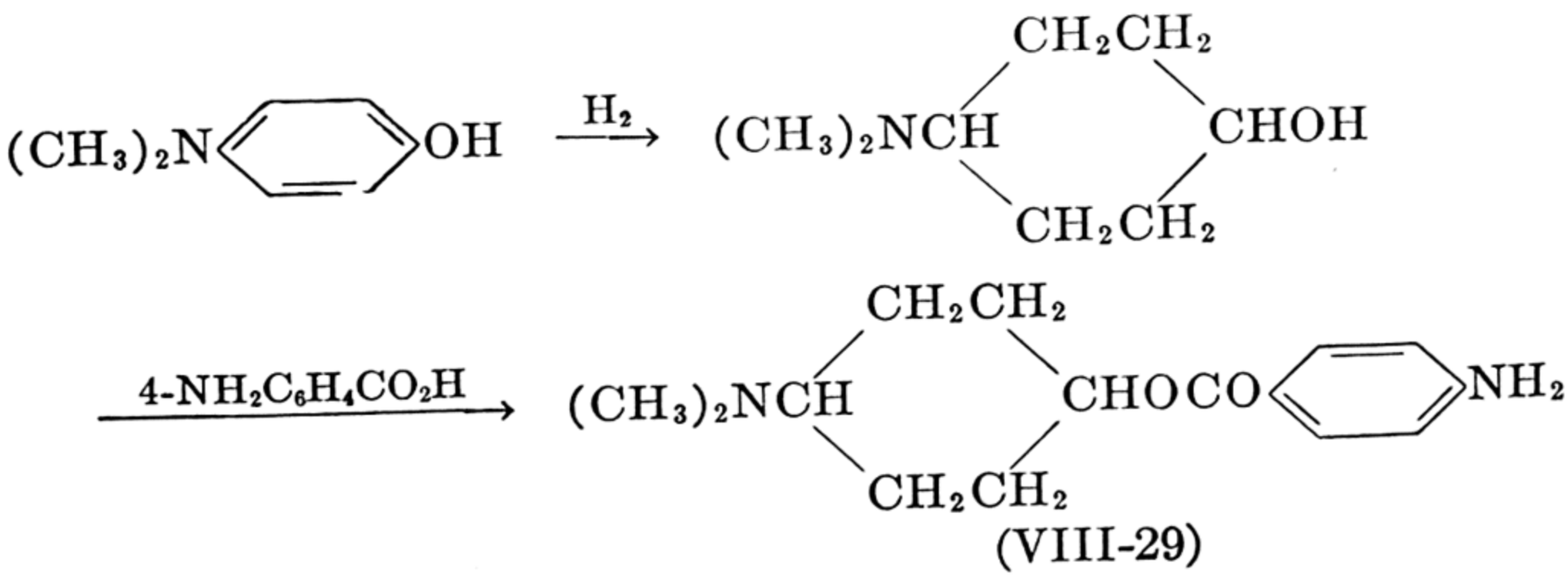
(VIII-26): 2-$CO_2(CH_2)_nNR_2$
(VIII-27): 3-$CO_2(CH_2)_nNR_2$
(VIII-28): 4-$CO_2(CH_2)_nNR_2$

A definite arrangement of the effect of simple heterocyclic rings on local anesthetic activity can barely be given. The order of activity increases generally from furan through thiophene and pyrrole to benzene[29] but 2-furoates have been found more active than the corresponding benzoates in some instances.[30]

(b) Changes in the Side Chain

No systematic regularity governs the effect of the length of the alkylene chain separating the ester from the tertiary amino group. It seems that as in other series lengthening of the chain above two carbon atoms increases local anesthetic as well as general pharmacological activity, especially the toxicity of the compounds. Since most investigators have not gone beyond 2-, 3-, and 4-carbon systems, it is not possible to say whether a peak of activity might be reached at a higher number of carbon atoms. Branching of the alkylene chain has been attempted successfully in a number of cases. The compounds Tutocaine and Larocaine are witness of these experiments. Alypin has two amino groups on a symmetrically branched alkylene chain. No unusual properties can be attributed to this more strongly basic drug.

If the alkylene chain becomes part of a saturated ring system, geometrical isomerism of the resulting basic esters becomes possible. The *cis*-form of 4-dimethylaminocyclohexyl *p*-aminobenzoate (VIII-29), prepared from *p*-dimethylaminophenol by nuclear hydrogenation and esterification with *p*-aminobenzoic acid, is less active than the *trans*-isomer in tests on goldfish.[31] Incidentally, the 3-dimethylamino isomer is even more active

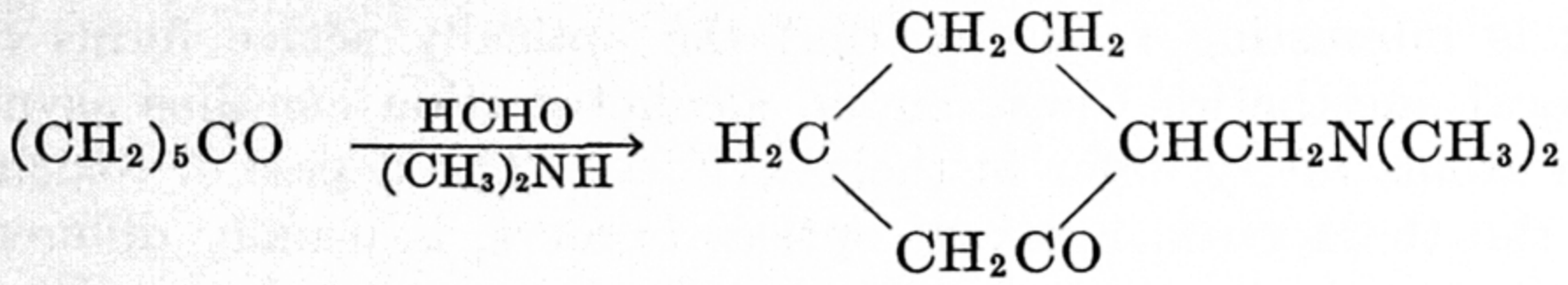


(VIII-29)

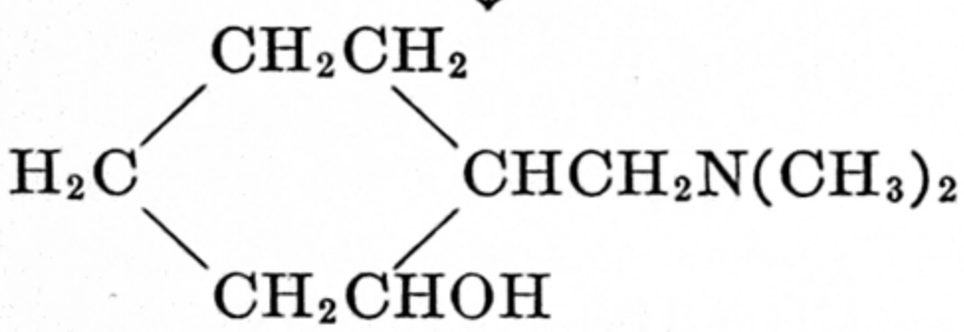
[29] Gilman and Pickens, *J. Am. Chem. Soc.*, **47**, 245 (1925).
[30] Cook and Kreke, *J. Am. Chem. Soc.*, **62**, 1951 (1940).
[31] Heckel and Adams, *J. Am. Chem. Soc.*, **49**, 1303 (1927).

than the *trans*-4-derivative, showing more than twice the local anesthetic effect of cocaine.

A Mannich reaction with secondary amines and cyclohexanone furnishes α-dialkylaminomethylcyclohexanones (VIII-30) which may be reduced to the corresponding secondary alcohols (VIII-31) which exist in

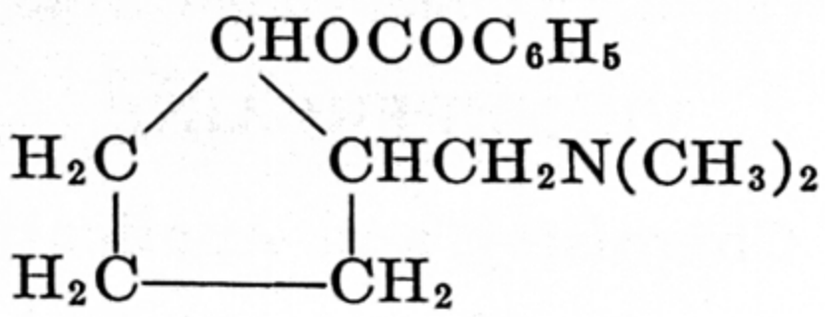


(VIII-30)



(VIII-31)

diastereoisomeric forms. Benzoylation of the dimethylamino-, diethylamino- or piperidino- derivatives yields diastereoisomeric compounds of which only one is very active.[32] Of the two racemic forms of the lower ring-homolog, 2-dimethylaminomethyl cyclopentanol benzoate (VIII-32) only one form has pronounced local anesthetic activity while the other racemic form is inactive.



(VIII-32)

There seems to be no well-defined relation between the structure of the amino group, and the local anesthetic activity of the drug. In the majority of the cases, tertiary amino groups with two equal alkyl groups have been used. Occasionally, mixed amines have been tested.[33] Cyclic tertiary amino groups appear in Methycaine, Surfacaine and similar compounds. Secondary amino groups are represented in monocaine, amylcaine and hexylcaine. Primary amino derivatives seem to be unstable as the free bases, the aroyl group shifting from the ester oxygen (VIII-33) to the primary nitrogen atom, giving a hydroxy-amide[34] (VIII-34).

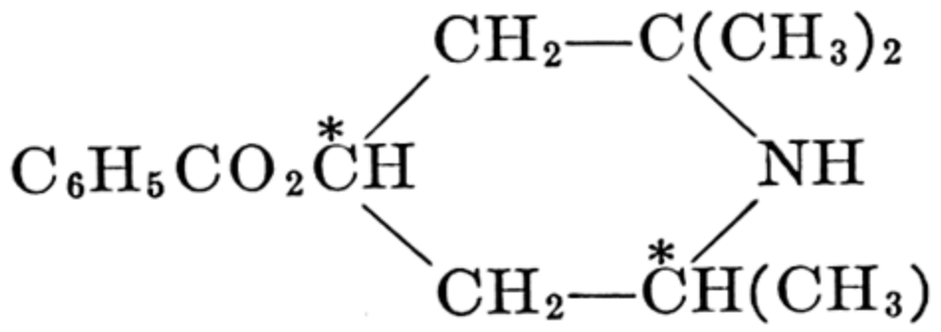
[32] Mannich and Hönig, *Arch. Pharm.*, **265**, 598 (1927).
[33] Brill, *J. Am. Chem. Soc.*, **54**, 2484 (1932).
[34] Hartung, Munch, and Kester, *J. Am. Chem. Soc.*, **54**, 1526 (1932).

$C_6H_5CO_2CH(C_6H_5)—CH(CH_3)NH_2 \rightarrow C_6H_5CHOHCH(CH_3)NHCOC_6H_4$

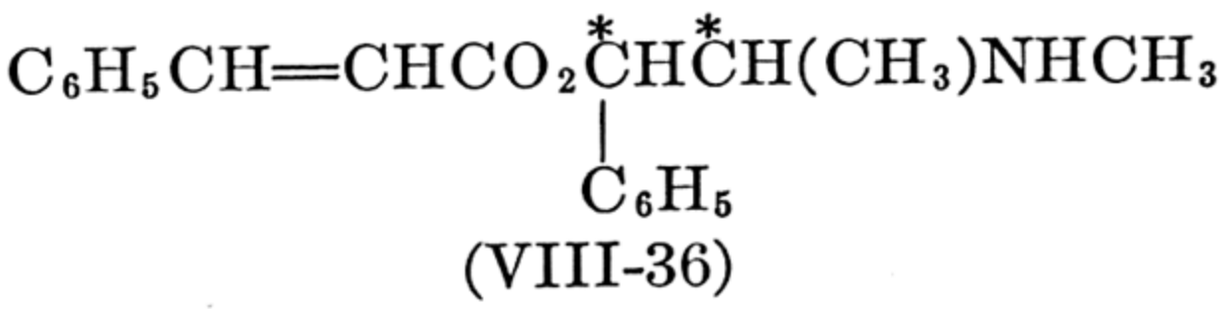
(VIII-33) (VIII-34)

(c) Steric Effects

It is interesting to notice that the optically active forms of ester type local anesthetics whose amino alcohol portion contains asymmetric carbon atoms rarely differ in their activity. The degree of toxicity, and hence the therapeutic index of optical isomers, is usually different, but not their medicinally valuable action. The two racemic forms of β-eucaine (VIII-35) for example, have a somewhat differing local anesthetic activity but this does not hold for the respective (+)- and (−)- forms.[35]



(VIII-35)



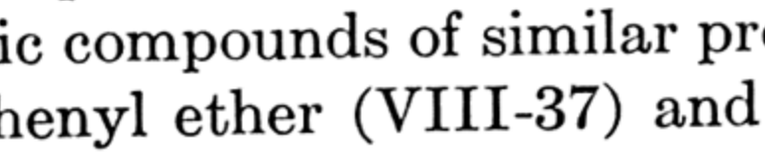
(VIII-36)

A similar condition prevails for the optical isomers of the powerful, although irritating, anesthetic cinnamylephedrine (VIII-36).[36]

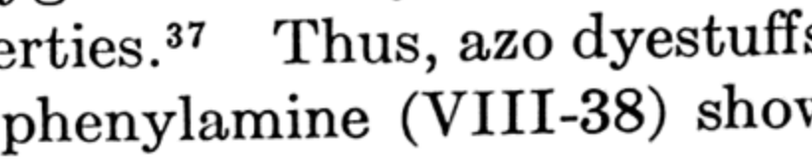
VI. NUPERCAINE

1. Chemistry and Application

The replacement of functional oxygen atoms by imino group can lead to isosteric compounds of similar properties.[37] Thus, azo dyestuffs derived from diphenyl ether (VIII-37) and diphenylamine (VIII-38) show similar



(VIII-37)

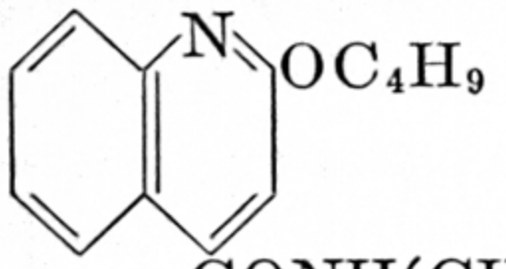


(VIII-38)

absorption spectra. A similar comparison may be drawn between esters and amides, RCOOR′ and RCONHR′. These types are related by their reversible mode of formation by alcoholysis and ammonolysis, respectively,

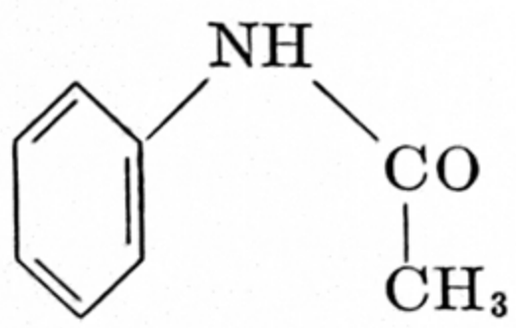
[35] King, *J. Chem. Soc.*, **125,** 41 (1924).
[36] Schultz and Barbour, *J. Pharmacol. Exptl. Therap.*, **76,** 295 (1942).
[37] Grimm, Günther, and Tittus, *Z. physik. Chem.*, **14,** 169 (1931).

their ability to undergo hydrolysis, and other chemical similarities. Frankland even regarded amides as ammono esters. It could be expected that amides containing groups comparable to the local anesthetic esters would exert a similar action. The series of dialkylaminoalkyl amides of 2-alkoxycinchoninic acids culminating in Nupercaine (dibucaine hydrochloride, VIII-39) has borne out this prediction.

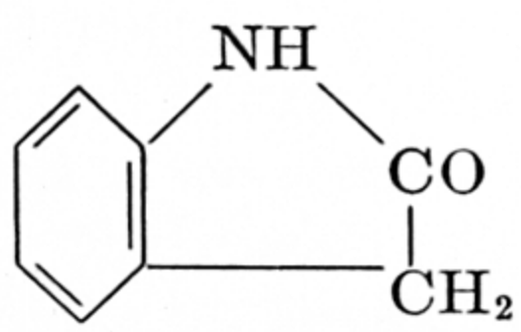


(VIII-39)

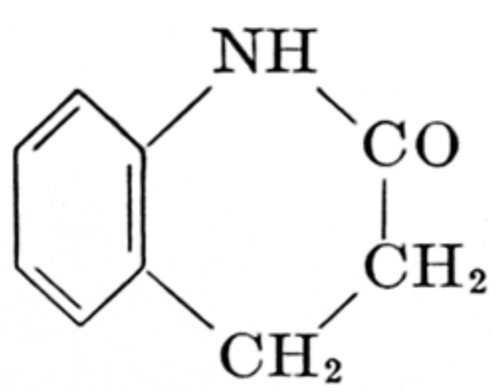
As it has been the case so often in the history of medicinal chemistry, Miescher[2] arrived at the synthesis of Nupercaine (called percain in Europe) by a route not at all concerned with the logical deductions outlined above. Searching for antipyretics in the acetanilide series (VIII-40), the analogous cyclic compound, oxindole (VIII-41), and its ring homolog, dihydrocarbostyril (VIII-42) were tested. Since the latter exhibited narcotic proper-



(VIII-40)

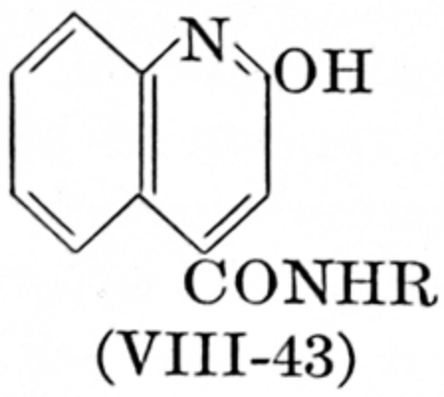


(VIII-41)

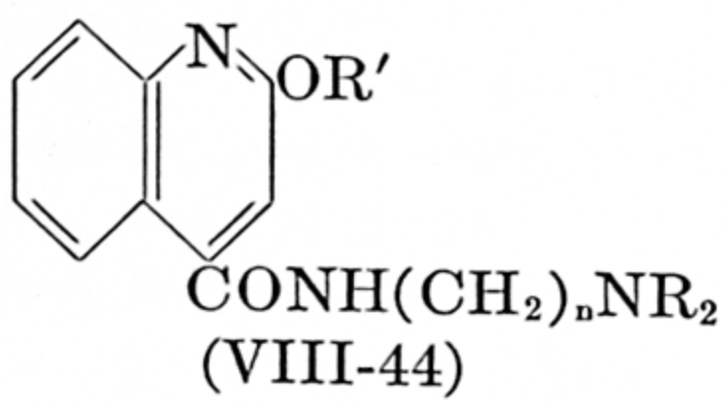


(VIII-42)

ties, derivatives of carbostyril carboxylic acids in which the acidic function is weakened by amidation were studied (VIII-43). It was thought that



(VIII-43)



(VIII-44)

such amides would revert formally to the acetanilide type and therefore lead again to antipyretics. In the course of this work, screening tests for other activities were carried out to complete the pharmacological study of this series, and it was discovered that etherification of the 2-hydroxyl group, and substitution of the amide group by basic radicals no longer produced antipyretics but long-lasting, although rather toxic local anesthetics (VIII-44). Nupercaine (VIII-39) produces local (including topical) anesthesia for two hours in a dilution of 1:120,000 as compared with 1:1000 for cocaine, or 1:2000 for procaine. Notwithstanding its relatively

high toxicity, these properties have assured Nupercaine a place in clinical usage.

For the synthesis of Nupercaine, isatin (VIII-45) is converted to carbostyril-4-carboxylic acid (VIII-46) by ring enlargement of its *N*-acetyl derivative. Phosphorus pentachloride furnishes 2-chlorocinchoninyl chloride (VIII-47) which reacts with unsymmetrical diethyl-ethylenediamine to give the basic amide (VIII-48). Etherification with sodium *n*-butoxide leads to the base of the drug.

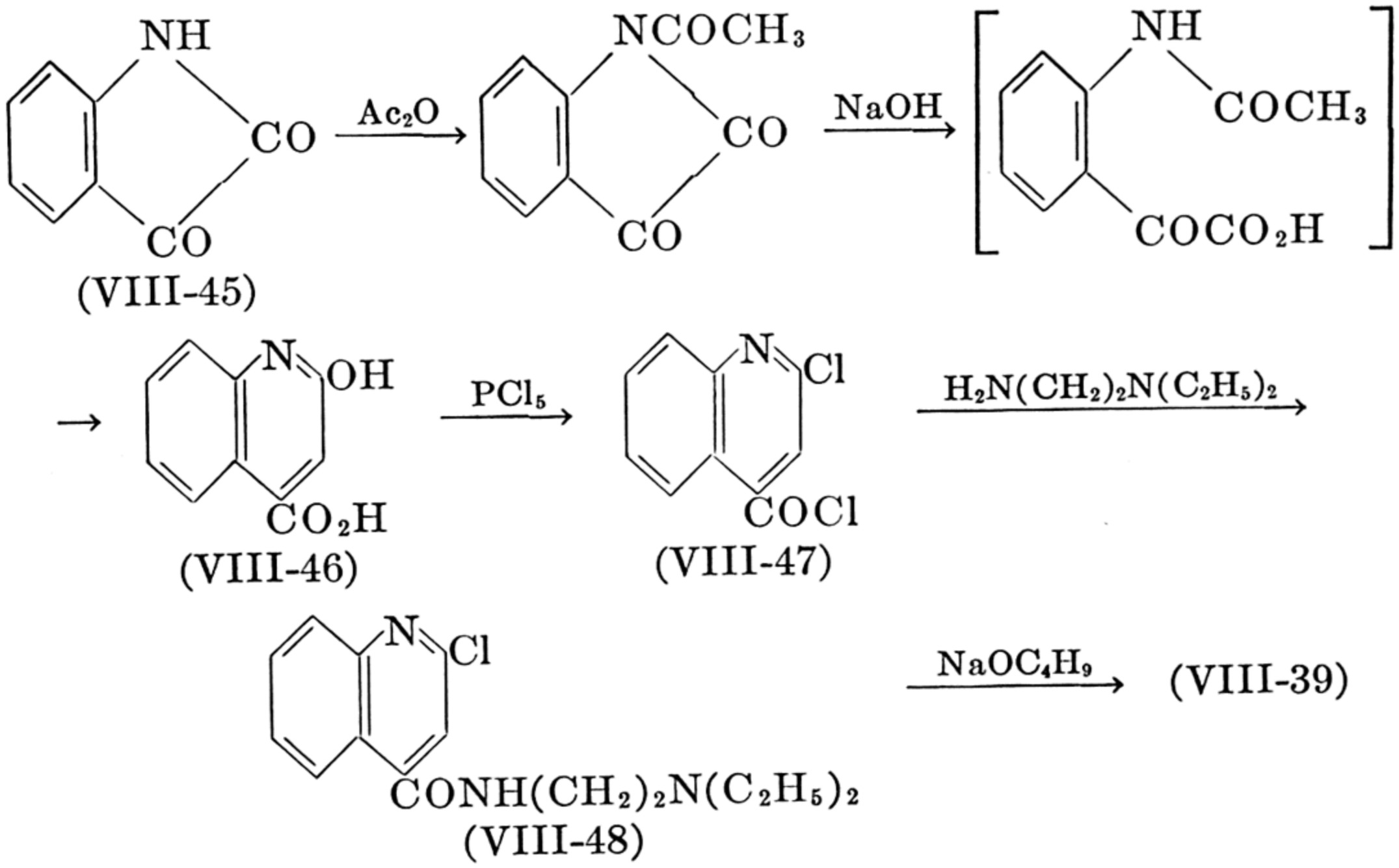


Figure 3. Synthesis of Nupercaine[2]

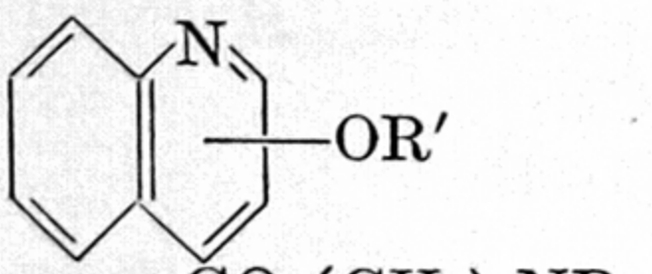
In an attempt to correlate certain physical properties of Nupercaine with its local anesthetic activity, the surface tension of its solutions at different dilutions was compared with pharmacological effectiveness. Based on the theory of Traube[38] that a compound will accumulate at cell surfaces, and thereby facilitate its absorption by the cell the more it depresses the surface tension of water, the number of drops of constant volumes of Nupercaine solutions falling from a stalagmometer were measured. This number is inversely proportional to the surface tension. These experiments demonstrated the enhanced activity of the free base over the hydrochloride, and showed that among Nupercaine homologs a maximum is attained for the 2-butoxy group. However, maxima of surface-

[38] Traube, *Biochem. Z.*, **98,** 177 (1919); *Arch. ges. Physiol.* (*Pflügers*), **218,** 749 (1928).

tension depressing properties at a higher number of carbon atoms in the alkoxy group could be predicted by extrapolation; the observed lower anesthetic activity of such compounds may, perhaps, be explained on the basis of their decreased solubility; this cancels the effect of the greater surface properties on the rate of absorption by the cell.

2. Similar Amides and Esters

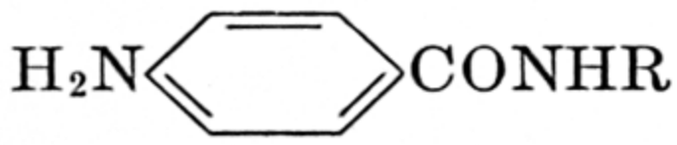
In dialkylaminoalkyl esters of alkoxycinchoninic acids (VIII-49) corresponding to Nupercaine maximum activity is noted again in 2-butoxy derivatives, but the position of the alkoxyl group is of little consequence.[39]



(VIII-49)

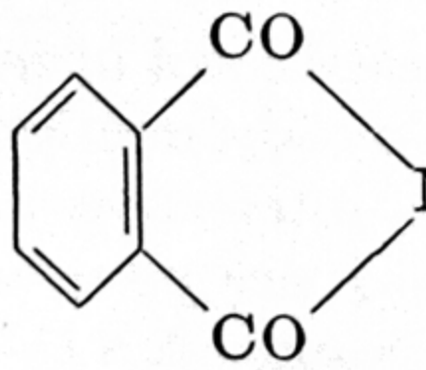
$C_6H_5CONH(CH_2)_nNR_2$

(VIII-50)



(VIII-51)

The discovery of the local anesthetic activity of Nupercaine and its analogs led to a thorough investigation of other amides, as well as urethans and amidines. Attention was directed first upon benzamides in which the amide group was substituted by dialkylaminoalkyl radicals (VIII-50),[40] but stronger surface anesthetics are created if the basic function of such side-chains is transferred to the nucleus (VIII-51), provided the alkyl group contains four to eight carbon atoms.[41] Other amides derived from naphthoic[42] and cinnamic acids[43] have also proved useful. The aromatic nuclei present in these compounds may not even be necessary to bring about anesthetic properties since monomethyl amides of seven- to nine-carbon aliphatic acids are also active.[44] N-Dialkylaminoalkyl phthalimides (VIII-52) have also been recommended.[45]



(VIII-52)

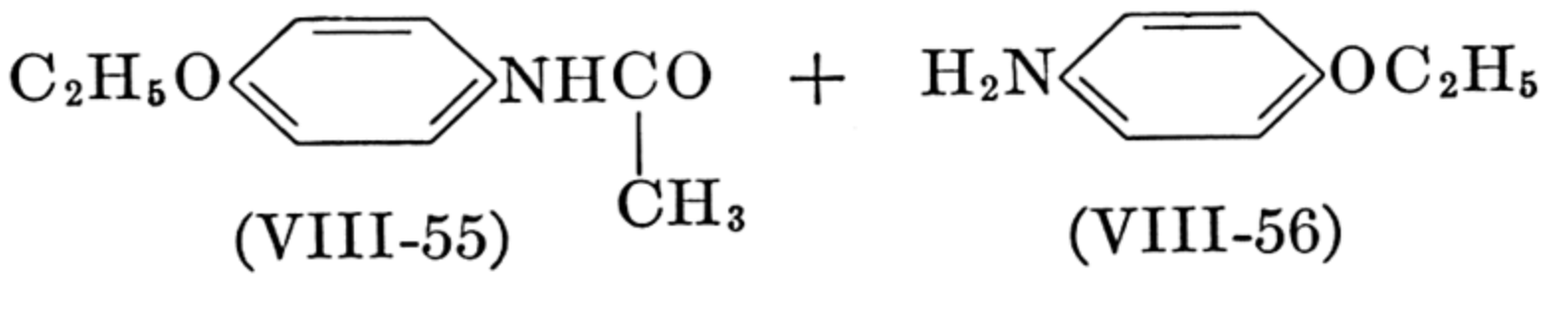
$C_6H_5NHCONHCH(CH_3)CH_2N(C_4H_9)_2$

(VIII-53)

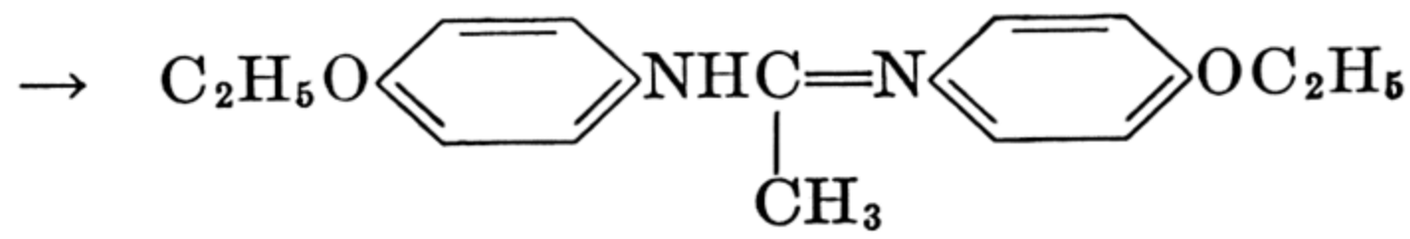
[39] Wojahn, *Arch. Pharm.*, **269,** 422 (1931).
[40] Eisleb, U. S. Pat. 2,073,100 (1937).
[41] Wenker, *J. Am. Chem. Soc.*, **60,** 1081 (1938).
[42] Blicke, Parke, and Jenner, *J. Am. Chem. Soc.*, **62,** 3316 (1940).
[43] Lott, U. S. Pat. 2,139,687 (1938).
[44] d'Alelio and Reid, *J. Am. Chem. Soc.*, **59,** 109 (1937).
[45] Moore, U. S. Pat. 2,343,198 (1944).

3. Ureas, Amidines, Guanidines

From substituted amides, the next step led to basically substituted ureas one of which (VIII-53) was anesthetic when placed on the tongue.[41] Likewise, substituted amidines have been tested; the best-known drug of



(VIII-55) (VIII-56)

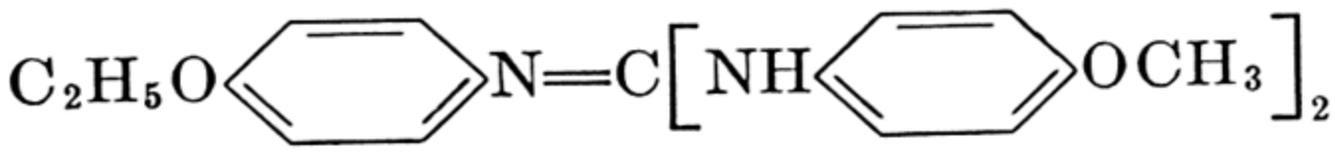


(VIII-54)

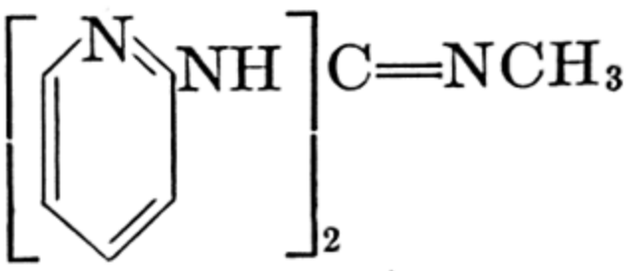
this group is Phenacaine (holocaine, VIII-54). Because of its relatively high systemic toxicity it is used preferentially as a surface rather than as an infiltration anesthetic. It is synthesized by condensation of acetophenetidine (VIII-55) with *p*-phenetidine (VIII-56).

The discovery of the local anesthetic activity of Phenacaine was incidental to tests for its antineuralgic properties which grew out of the study of phenetidines in an approach similar to that outlined for Nupercaine.

At least one guanidine derivative, the drug acoin (VIII-57), has been introduced into clinical use as an infiltration anesthetic.[46] Several other



(VIII–57)



(VIII-58)

aromatically or heterocyclically substituted guanidines possess local anesthetic properties. The drug protocaine (VIII-58, di-(2-pyridyl)methyl guanidine) may serve as an example for this group. It is interesting to notice that certain other substituted α-aminopyridines which are used as antihistaminic agents (Neoantergan, Pyribenzamine; see Chapter XXIV) also exert definite topical local anesthetic activity.

4. Urethans

Since urethans are general cell depressants (Chapters XI and XXVII) the exhibition of local anesthetic properties by certain compounds in this group is not surprising. Their structure which combines amide and ester

[46] Hess and Trolldiener, *Therap. Monatshte.*, **1899**, 36.

functions at the same carbon atom relates them chemically to the substances described in this Chapter.

Diurethans of the formula $ROCONHCH_2CH_2NHCOOR$ in which R are simple alkyl groups anesthetize the rabbit cornea.[47] The usefulness of urethan anesthetics is greatly enhanced, however, by incorporation of aminoalkyl radicals in the ester portion of the carbamates. The drug Diothane (VIII-59), the di-N-phenylcarbamate of 1-piperidinopropane-2,3-diol produces long-lasting anesthesia and has been used in such surgical procedures as amputations. It may be synthesized from 1-piperidino-2,3-propanediol (VIII-60) and phenylisocyanate.[48]

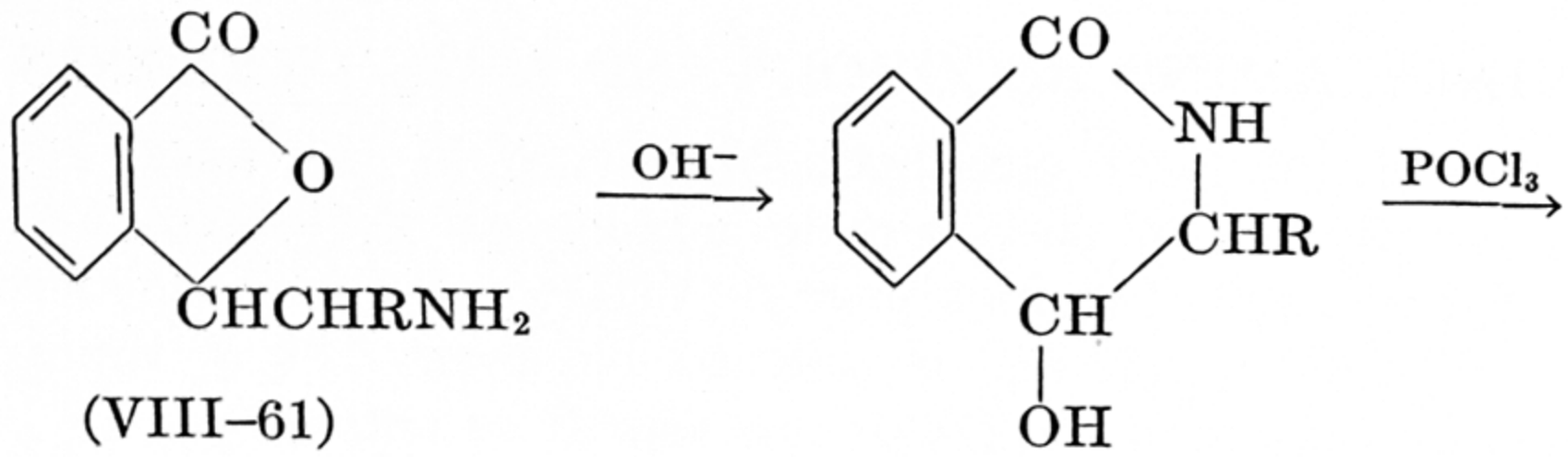
$HOCH_2CHOHCH_2NC_5H_{10}$

(VIII-60) $\xrightarrow{C_6H_5NCO}$ $C_6H_5NHCO_2CH_2CHCH_2NC_5H_{10}$ with $OCONHC_6H_5$ on the CH

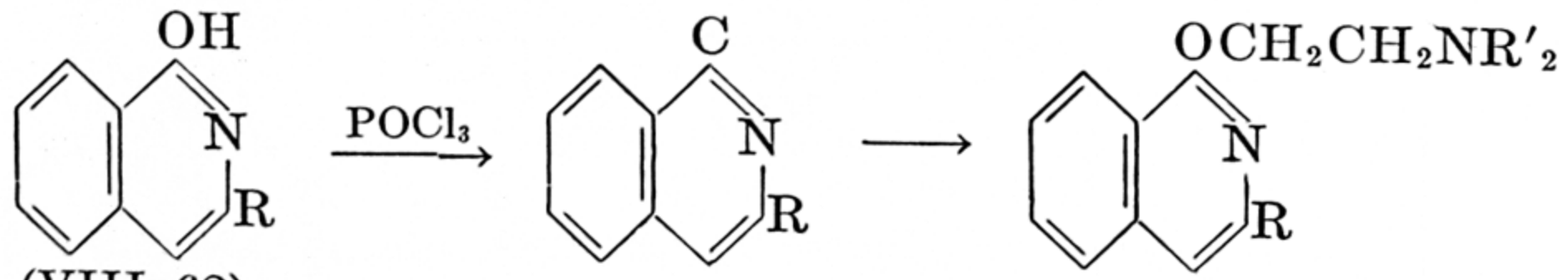
(VIII-59)

VII. ALKYLISOQUINOLINE AMINOALKYL ETHERS

In the course of studying a series of aminoalkylphthalides (VIII-61) (Chapter XI), a rearrangement of these compounds to 1-hydroxy-3-alkylisoquinoline derivatives (VIII-62) was observed.[49] From these intermediates, the corresponding 1-dialkylaminoalkyl-3-alkylisoquinolines (VIII-63) were prepared by the accompanying scheme.



(VIII–61)

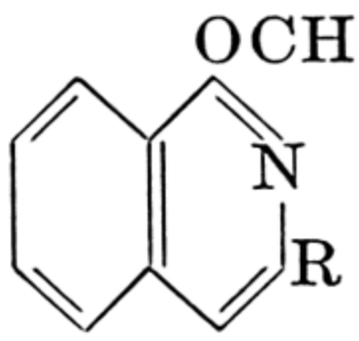


(VIII–62) (VIII–63)

[47] Ma and Shriner, *J. Am. Chem. Soc.*, **58,** 1630 (1934).
[48] Rider, *J. Am. Chem. Soc.*, **52,** 2115 (1930). Raasch and Brode, *J. Am. Chem. Soc.*, **64,** 1112 (1942).
[49] Ullyot, Stehle, Zirkle, Shriner, and Wolf, *J. Org. Chem.*, **10,** 429 (1945).

Of these compounds, the 3-*n*-butyl derivative (R = C_4H_9; R′ = C_2H_5) produces long-lasting topical local anesthesia. A structural comparison with Nupercaine is inevitable because the latter with its butoxy group also represents the optimal drug in its own series. The butyl compound of the general formula (VIII-63) is about three times more effective and 1.5 times less toxic than dibucaine.[50] Length of action in this series parallels increasing solubility in oils as shown in Table II.

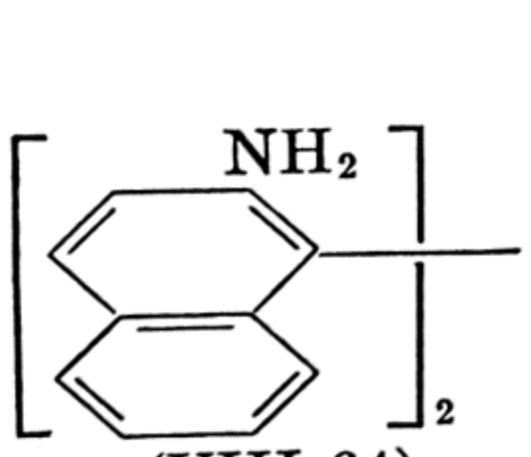
TABLE II. Relation of Duration of Local Anesthetic Activity of Dialkylaminoaklyl Isoquinoline Ethers to Distribution between Water and Oil



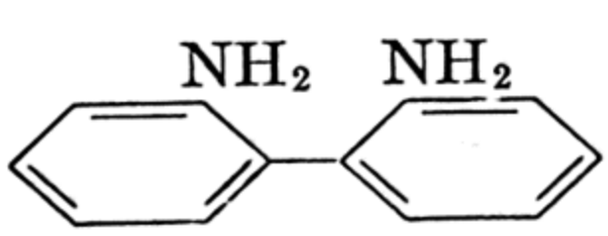
R =	C = $\frac{\text{Con. in water}}{\text{Con. in oil}}$	Duration of action, min.
H	—	10
CH_3	22.3	76
C_2H_5	3.5	121
C_3H_7	3.0	180
C_4H_9	0.97	514

VIII. AMINES, AMINO ALCOHOLS AND AMINO KETONES

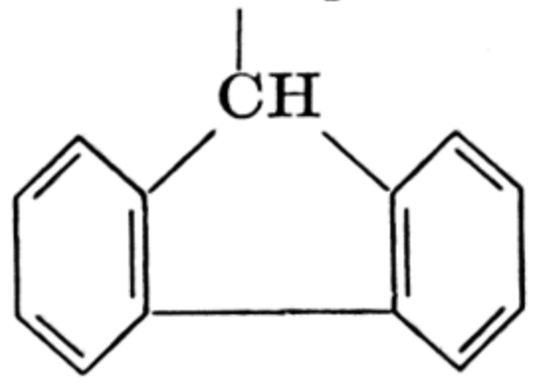
The occurrence of local anesthetic properties in the most varied structures is manifested in such simple amines as 2,2′-diamino-1,1′-binaphthyl (VIII-64), 2,2′-diaminobiphenyl (VIII-65) and 9-aminofluorene (VIII-66). Compound (VIII-65) is said to be about thirty times as active as cocaine, compound (VIII-66) one fourth as active.[51]



(VIII-64)



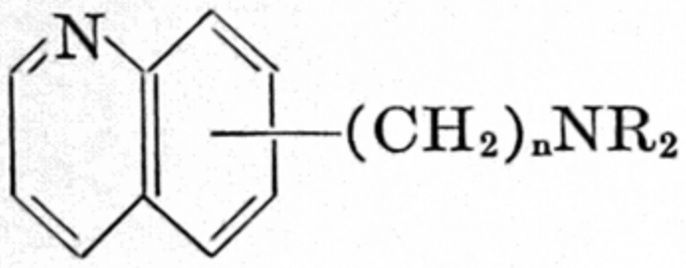
(VIII-65)



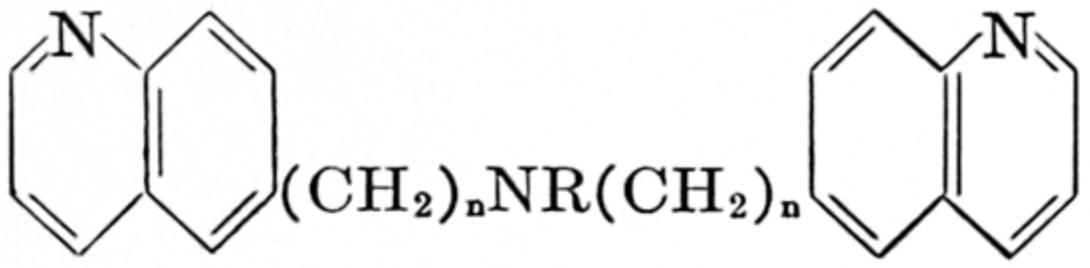
(VIII-66)

[50] Wilson, Dawson, Brooks, and Ullyot, *J. Am. Chem. Soc.*, **71,** 937 (1949). Fellows and Macko, *Federation Proc.*, **8,** 291 (1949).

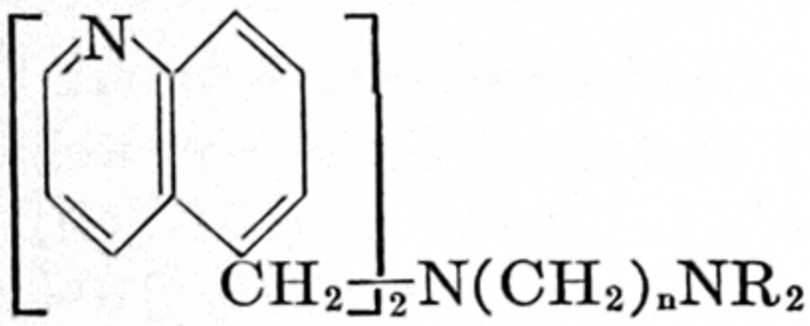
Powerful local anesthetics have been observed among substituted amino derivatives of heterocyclic systems. α-Aminopyridines,[52] dialkylaminoalkylquinolines[53] (VIII-67, 68, 69), and aminomethylquinolines (VIII-70) have shown marked activity. The position of the basic side chain may be of significant influence since the isomeric 2-butoxy-3-aminomethyl quinoline (VIII-71) is inactive.



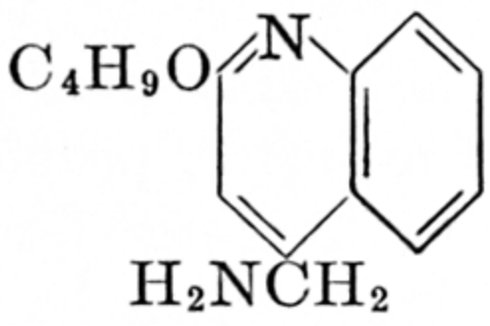
(VIII-67)



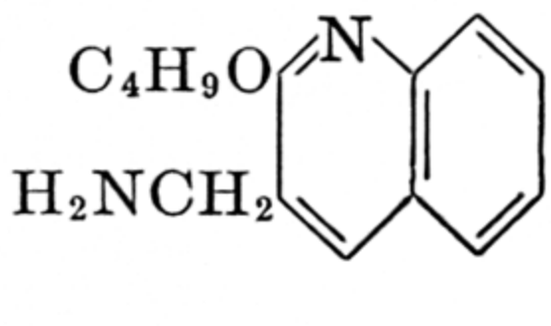
(VIII-68)



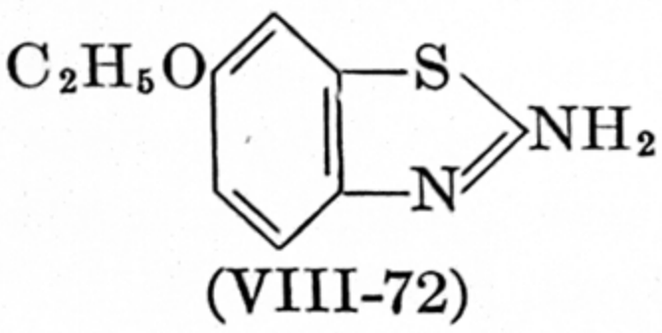
(VIII-69)



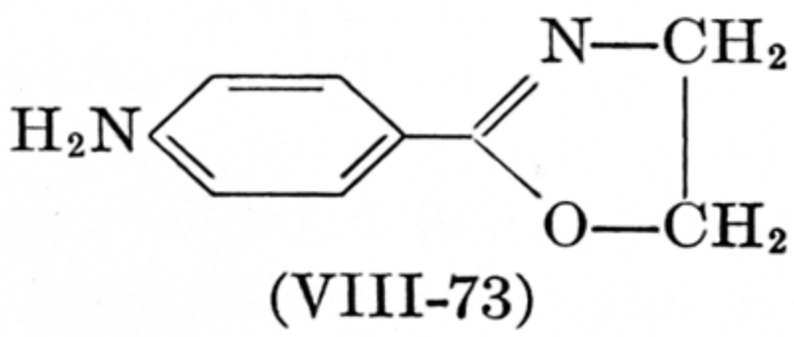
(VIII-70)



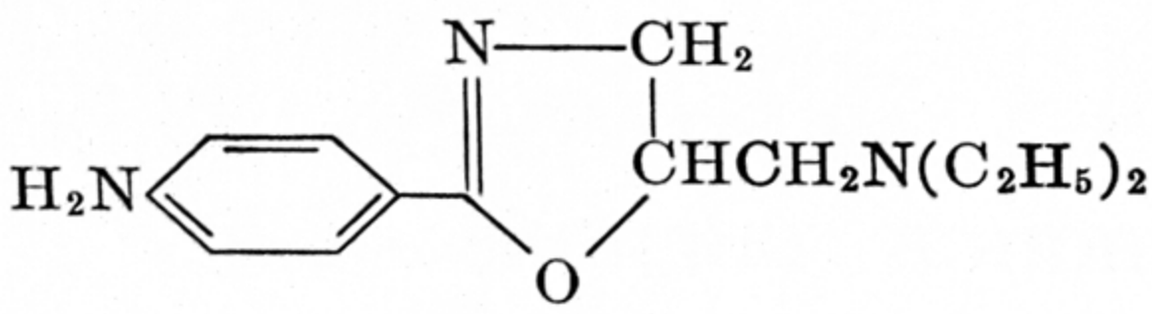
(VIII-71)



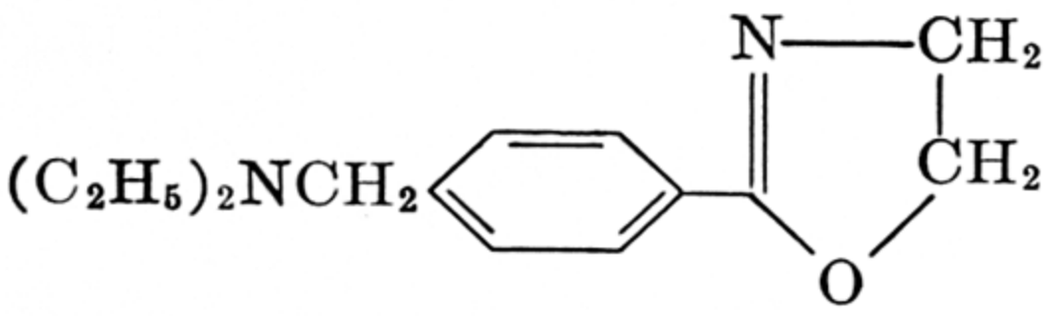
(VIII-72)



(VIII-73)



(VIII-75)



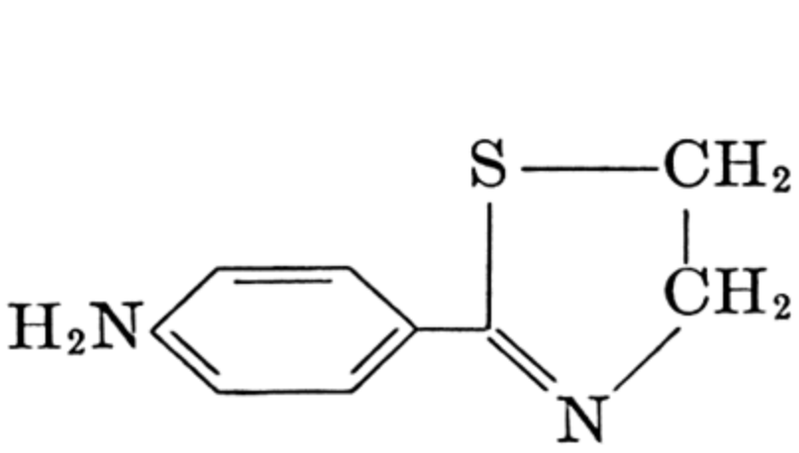
(VIII-74)

[51] Supniewski and Gajewska, *Acta polon. pharmac.*, **3,** 97 (1939); *Chem. Zentr.*, **1939,** *II*, 2444. Chierici, *Ann. chim. farm.*, **1938,** 48; *Chem. Zentr.* **1939,** *II*, 175.

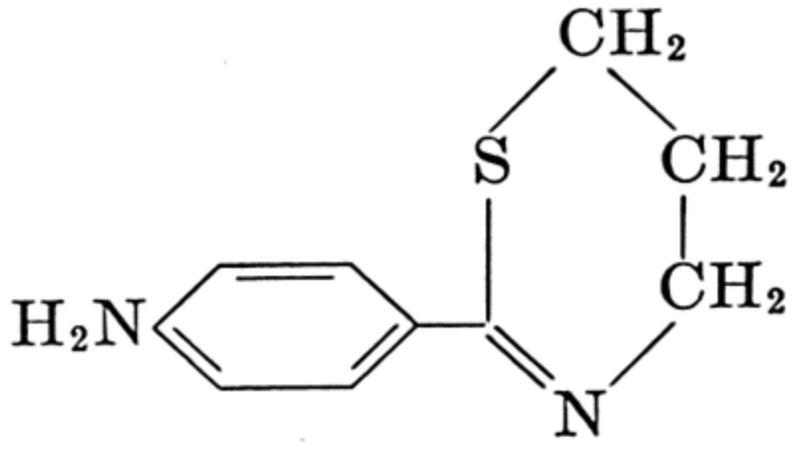
[52] Chichibabin and Bylinkin, *Ber.*, **55,** 998 (1922). Seide, *Ber.*, **57,** 1802 (1924). Pitini, *Ann. chim. applicata*, **2,** 213 (1914); *Chem. Abstr.* **9,** 485 (1915).

[53] Kermack, Wright and Muir, *J. Chem. Soc.*, **1935,** 1143, 1421. Sinha, *J. Pharmacol. Exptl. Therap.*, **58,** 62 (1936). Wojahn and Kramer, *Arch. Pharm.*, **276,** 291, 303 (1938).

Other heterocyclic amines exhibiting activity include 2-amino-6-ethoxybenzothiazole[54] (VIII-72), the aminophenyl-2-oxazolines (VIII-73, 74 and 75) as well as *p*-aminophenyl substituted thiazolines (VIII-76) and thiazines (VIII-77), 2-pentoxazolines, oxazoles, thiazoles and similar compounds.[55]

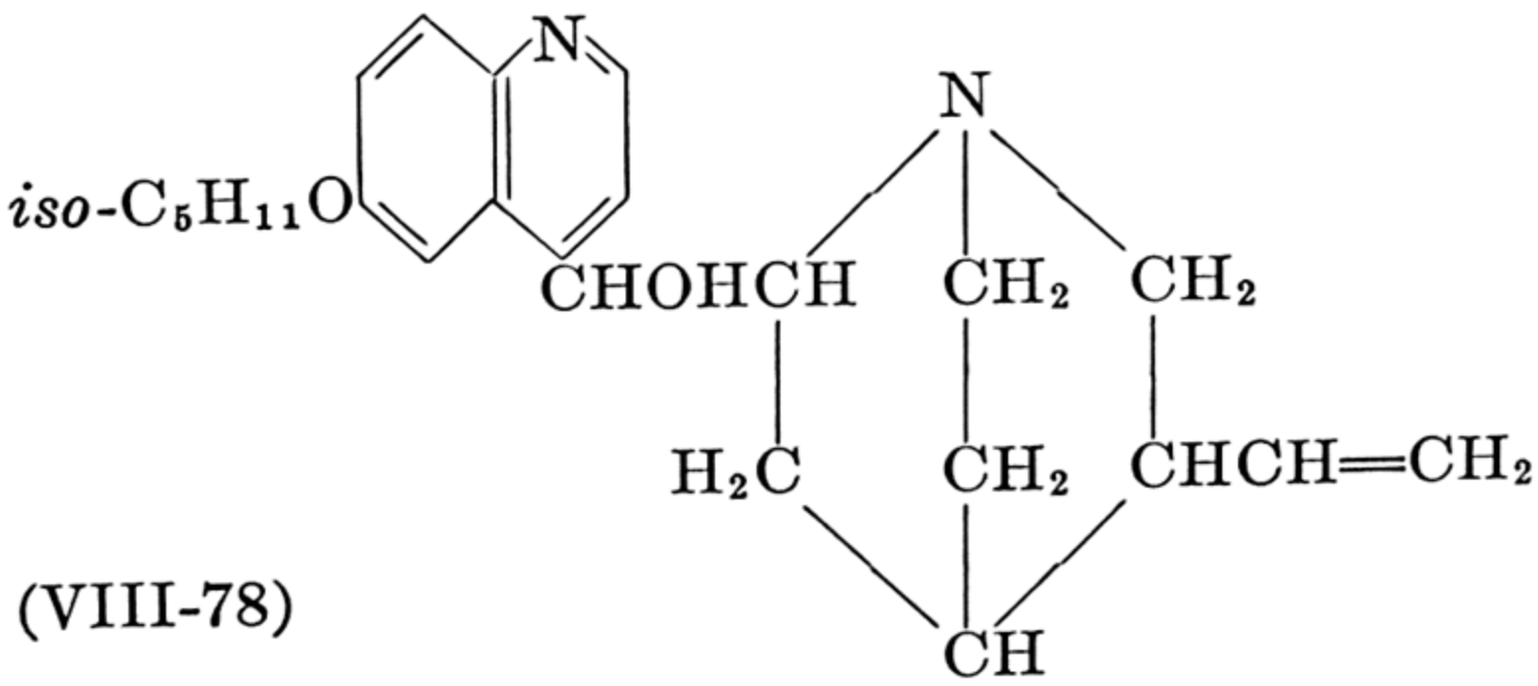


(VIII-76)



(VIII-77)

Simple amino alcohols may produce local anesthesia without being part of the molecule of an ester, provided that their molecular weight is sufficiently high. Thus, 3-amino-6-methyl-heptanol-4 [$(CH_3)_2CHCH_2$-$CHOHCH(C_2H_5)NH_2$] and 1-phenyl-2-aminopentanol-1 [$C_6H_5CHOHCH$-$(NH_2)CH_2CH_2CH_3$] show definite activity.[56] However, deficiencies in molecular weight and lipid-water distribution coefficients of such amino alcohols are more readily overcome as lighter compounds in this group are esterified with increasingly heavier acyl portions. The acetate of diethylaminoethanol is still inactive while its trichloroacetate, acrylate, or dimethylacrylate esters exhibit local anesthetic properties.[57]



(VIII-78)

If the amino alcohol has a sufficiently high molecular weight, as in isoamylhydrocupreine (Eucupin, VIII-78) esterification is no longer neces-

[54] Ballowitz, *Arch. exptl. Path. Pharmakol.*, **163,** 687 (1931).

[55] Leffler and Adams, *J. Am. Chem. Soc.*, **59,** 2252 (1937). Babcock and Adams, *J. Am. Chem. Soc.*, **59,** 2260 (1937). Novelli and Adams, *J. Am. Chem. Soc.*, **59,** 2259 (1937). Friedman, Sparks, and Adams, *J. Am. Chem. Soc.*, **59,** 2262 (1937).

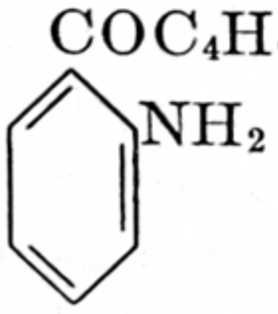
[56] Kanao, *J. Pharm. Soc. Japan*, **49,** 173 (1929).

[57] Gilman, Herkert, and McCaracken, *J. Am. Chem. Soc.*, **50,** 437 (1928).

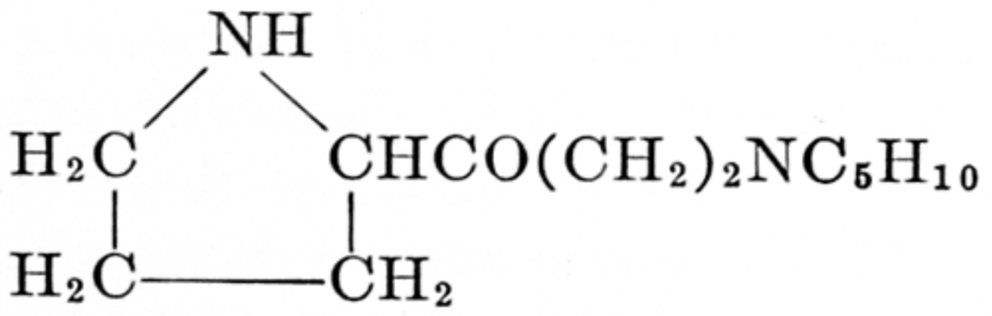
sary to produce even prolonged and useful local anesthetic action. However, even diethylaminoethanol produces obtusion to pain, when injected intravenously but this activity must be classified as analgetic (Chapter XI).

If one considers the role of acetylcholine and epinephrine in the transmission of nervous impulses, the possibility of regarding amino alcohols and their esters as analogs, or perhaps antagonists of the natural hormones becomes apparent. It could be assumed that local anesthetics would compete with acetylcholine for a place in cholinesterase-catalyzed systems and thereby interfere with the normal catalytic reactions of the enzyme. Pharmacological evidence supports this mechanism of local anesthetic action; *in vitro* inhibition experiments of cholinesterase by some of the common local anesthetics parallels in general their anesthetic potency.[58]

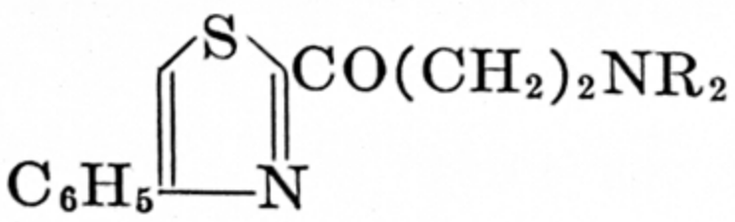
Among amino ketones which have been found to possess local anesthetic properties the following examples may be mentioned: *o*-aminovalerophenone (VIII-79),[59] 2-(3-piperidino)propionyl pyrrolidine (VIII-80),[60] β-dialkylaminothiazolyl (VIII-81) and -oxazolyl ketones (VIII-82).[61] Particularly aminoketones in the carbazole series (VIII-83) are powerful anesthetics.[62]



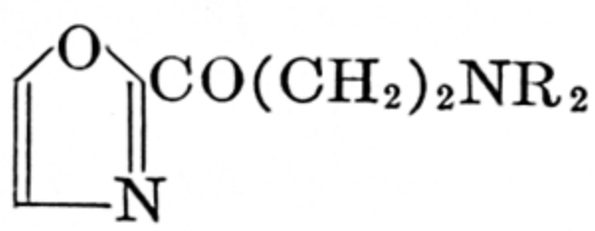
(VIII-79)



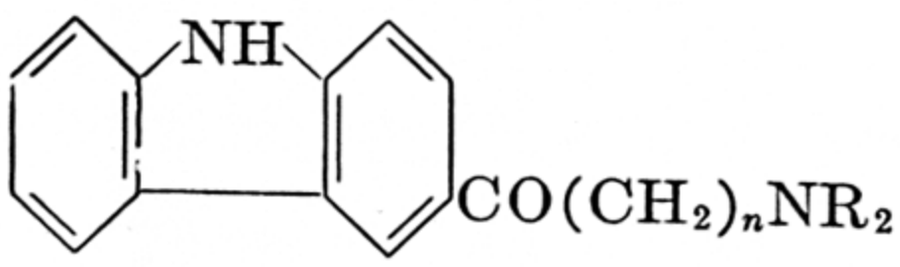
(VIII-80)



(VIII-81)



(VIII-82)



(VIII-83)

[58] Bullock, *Quart. J. Pharm. Pharmacol.*, **21,** 266, 407 (1948).
[59] Hartung and Munch, *J. Am. Chem. Soc.*, **51,** 2570 (1929).
[60] Morgenroth, *Ber. ges. Physiol. u. exptl. Pharmakol.*, **27,** 367 (1917); **29,** 233 (1919).
[61] Levvy and Nisbet, *J. Chem. Soc.*, **1938,** 1572; *J. Pharmacol. Exptl. Therap.*, **65,** 129 (1939).
[62] Gaind, Ray, and Sarin, *J. Indian Chem. Soc.*, **17,** 619 (1941); *Chem. Abstr.* **36,** 5176 (1942).

IX. NITROGEN-FREE LOCAL ANESTHETICS

The most important non-nitrogenous local anesthetic is benzyl alcohol.[63] It is soluble to the extent of 4% in water and produces topical anesthesia in this concentration, or in ointments or lotions. Its application is often followed by local irritation; because it is readily oxidized to benzoic acid in the body and excreted as hippuric acid its use has remained limited to the relief of burns or cutaneous itching.

o-Hydroxybenzyl alcohol (saligenin, salicyl alcohol) has been used in a similar manner. It is relatively non-toxic and has been used also to anesthetize the urethric tract. Its pain-relieving properties have been attributed, in part, to its structural relation to the analgetic and antipyretic salicylates. As a matter of fact, the isolation of saligenin from the hydrolytic products of its glucoside, salicin, from the bark of the willow *Salix alba*, marked the opening of the investigation of salicylates as medicinals.

Occasional mention has been made of the local anesthetic properties of phenethyl alcohol ($C_6H_5CH_2CH_2OH$) and benzoyl carbinol ($C_6H_5COCH_2OH$) which probably owe their relatively low toxicity to the ease with which they are oxidized to benzoic acid *in vivo*.

Lower aliphatic alcohols, especially ethyl and isopropyl alcohol, are being used as rubbing alcohols for the relief of local neuralgias. As in other series, this low-grade effect is heightened by an increase in molecular weight. Chloretone [$(CH_3)_2C(OH)CCl_3$] has been found to possess definite local anesthetic properties. Menthol and octyl alcohols have been used for the same purpose.

[63] Macht, *J. Pharmacol. Exptl. Therap.*, **11**, 263 (1918).

CHAPTER IX

Hypnotics and Sedatives

The physiology of normal sleep is not well understood. Slight depression of respiration and blood-pressure, and equally slight changes in the concentration of potassium and other cations in the blood are among the few indistinct symptoms which have been observed. There are many conditions which prevent normal sleep. External stimuli such as noise, the unaccustomed motion of a train or airplane, nervous irritation resulting from mental anguish or overwork, pain and maniacal states are among the best-known causes of insomnia. The logical way to help sleepless individuals may be the removal of the causative condition, that is, restoration of health in case of painful disease, establishment of quiet, restful surroundings, and relief from nervous tension. However, it is not always possible to reestablish such favorable conditions quickly, and relief from insomnia and the accompanying aggravation of its cause may have to be sought in symptomatic treatment. The role of the hypnotics starts at this point.

Hypnotics are depressant drugs which produce sleep. Their name is derived from the Greek *ὑπνός* (sleep), and the noun hypnosis expresses their activity. Hypnotics are used to induce sleep where natural sleep cannot be obtained. Some of them are so rapid in the onset of their action that they have to be administered to reclining patients in order to avoid accidents when the individual falls asleep virtually immediately. Paraldehyde and chloral belong in this category. Others act slowly and may be administered so that they will only cause a calming effect, sedation, in small doses while larger amounts produce sleep of varying depth and duration.

I. TESTING METHODS

As degrees of sleep are difficult to measure in laboratory animals, the amount of a compound which causes certain reflexes to disappear is frequently used to evaluate hypnotic activity. If the ratio of minimum hypnotic dose to lethal dose is great enough, the drug may be tested therapeutically. This type of testing must be done in warm-blooded animals since the hypnotic index of the same drug usually is more favorable, and therefore misleading, in cold-blooded animals.

A typical test method consists of tickling the inside of the ear of an animal with a splint. The smallest amount of the drug which no longer

causes an animal to respond to this or similar annoying external stimuli is considered the minimum effective dose. If measured in n animals, the average is listed as MED_n, or as MED_{50}.

Rapidity and duration of action are readily observed in animals. These factors together with studies of the rate of elimination, acute and cumulative toxicity, the effect of the drug on circulation and other physiological functions must be ascertained before clinical trial.

II. EARLY HYPNOTICS

Throughout the middle ages and until the middle of the nineteenth century ethyl alcohol and opium were used to produce euphoric stupor and occasionally therapeutic sleep, especially in lieu of the then unknown surgical anesthesia. Inorganic bromides were introduced as sedatives about 1864, but when used as hypnotics in larger doses were found to produce intoxication (bromism). Five years later Liebreich discovered the sleep-producing properties of chloral, and this was followed by paraldehyde, sulfonal and by urethan. In 1903, Emil Fischer and von Mering[1] varied the structure of barbituric acid which had been discovered by Baeyer and named after a "Miss Barbara",[2] and introduced Veronal (barbital) into medicine. From then on, hundreds of barbiturates have been tested as hypnotics. In addition, sleep-producing drugs have been found in many other groups of organic chemicals, especially among alcohols, aldehydes, amides, acylureas ($RCONHCONH_2$), alkylureas ($RNHCONH_2$), urethans ($ROCONH_2$), sulfones of the type $RR'(SO_2R'')_2$ and substituted biurets.

Even before enough statistical material had accumulated to permit generalizations, the variety of drugs capable of putting animals or persons to sleep led to the assumption that simple relations of structure and hypnotic activity would not suffice to explain the phenomenon of hypnosis by drugs. As will be seen, it has not yet been explained and presents a picture of ever-increasing complexity.

III. THE BARBITURATES

1. General

Of the various hypnotics available to the physician, the barbiturates hold a distinct therapeutic advantage. They are not disagreeable in taste like the otherwise excellent chloral and paraldehyde. Their use is not restricted to hypnosis but can be extended to sedation and anesthesia as well. On the whole, one-fourth or one-fifth of the hypnotic dose will

[1] Fischer and v. Mering, *Therap. Gegenwart*, **44**, 97 (1903).
[2] as told by Stadlinger, *Deut. Chem. Z.*, **1**, 49 (1949).

produce sedation within one to two hours which is a distinct advantage over the time-honored alkali bromides which require a much longer period for the same effect. Again the various classes of barbiturates permit a gradation of sleep production according to the needs of the patient. There are long acting, moderately long acting, short and ultra short acting barbiturates. Their duration and their onset of action accompanies the figures listed in Table I. In addition, they may be administered parenterally in emergencies and exhibit, in large enough doses, anticonvulsant activity. All the barbiturates are anticonvulsant but phenobarbital (IX-1) and a few N^1-alkyl derivatives such as Mebaral (IX-2) are distinguished by their special effect on the motor cortex which makes them useful in certain epileptic conditions.

The short-acting barbiturates as well as certain 2-thiobarbiturates, may be used to produce rapid surgical anesthesia of short duration. The main advantages of this application lie in emergency anesthesias, for example under war conditions, where portable or complex equipment is unavailable. The disadvantage of barbiturate anesthetics is particularly the impossibility of interrupting the anesthesia at any given point as can be done with volatile anesthetics. The barbiturates may also produce basal anesthesia prior to inhalation anesthesia, and they are widely employed as sedatives for pre-anesthetic medication. Moreover, barbiturates reduce the concentrations of ether and cyclopropane which produce anesthesia and respiratory arrest.

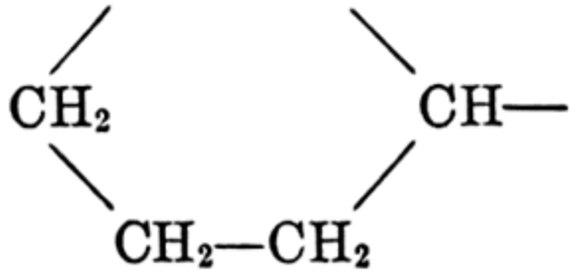
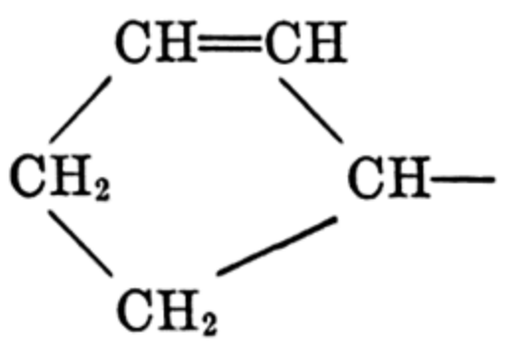
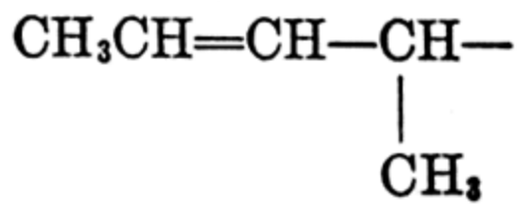
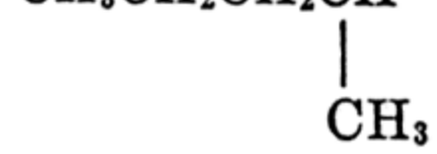
Toxic effects of local anesthetics may be averted prophylactically by barbiturates; especially the shorter acting members of this series can potentiate the analgetic effect of the salicylates, pyrazolones, and the *p*-aminophenol type analgetics, and are often used in combinations containing both types of drugs.

It has been proposed that the almost unnoticeably weak effects of the analgetics on the sleep center are raised in the presence of a true hypnotic. Vice-versa, morphine increases sharply the hypnotic action of barbiturates. Some of the combinations available in tablet form are listed in Table II.

The barbiturates act chiefly by depressing the central nervous system, especially the brain. The basal ganglia and the hypothalamus are first affected. The duration of this depression and the intensity of action depends on the structure of the drug, on its mode of administration and the amount used. Depression will be less when smaller doses are administered, and the same barbiturate can produce sedation or hypnosis depending on the dose.

The barbiturates have a quieting action in nervous and excited states, in manias, and in cases of hyperthyroidism, and since sleep under the influence of these drugs resembles natural dreamless sleep, large amounts

TABLE I. SUBSTITUTED BARBITURIC ACIDS

-barbituric acid	Synonyms	R^1	R^5	$R^{5'}$	Duration of action, hours	Onset of action, hours	Average adult hypnotic dose, g.
5,5′-Diethyl	Barbital	H	C_2H_5	C_2H_5—	4–12	0.5–1	0.3–0.5
5-Ethyl-5′-isopropyl	Ipral, Probarbital	H	C_2H_5	$CH(CH_3)_2$—	"	"	0.12–0.25
5-Ethyl-5′-*n*-butyl	Neonal	H	C_2H_5	*n*-C_4H_9—	"	"	0.05–0.1
5-Ethyl-5′-phenyl	Phenobarbital, Luminal (IX-1)	H	C_2H_5	C_6H_5—	"	"	0.1–0.2
5-Methyl-5′-phenyl	Rutonal	H	CH_3	C_6H_5—			
5-Allyl-5′-isopropyl	Alurate, Allonal, Numal	H	CH_2=$CHCH_2$	$CH(CH_3)_2$—	2–8	0.25–0.5	0.065–0.13
5-Ethyl-5′-isoamyl	Amytal	H	C_2H_5	$(CH_3)_2CHCH_2CH_2$—	"	"	0.1–0.3
5,5′-Diallyl	Dial, Curral	H	CH_2=$CHCH_2$	CH_2=$CHCH_2$—	"	"	0.1–0.3
5-Ethyl-5′-Cyclohex-enyl	Phanodorn	H	C_2H_5		"	"	0.1–0.2
5-Allyl-5′-Cyclohex-enyl	Khemital	H	CH_2=$CHCH_2$	dto.			
5-Allyl-5′-Cyclopen-tenyl	Cyclopal	H	CH_2=$CHCH_2$		"	"	0.12–0.25
5-Ethyl-5′-(1-methyl-butenyl)	Delvinal	H	C_2H_5		"	"	0.1–0.2
5-Ethyl-5′-*n*-hexyl	Ortal, Hexethal	H	C_2H_5	*n*-C_6H_{13}	"	"	0.2–0.4
5-(1-Methylbutyl)-5′-ethyl	Pentobarbital, Nembutal	H	C_2H_5		"	"	0.1–0.2

5-Allyl-5′-(1-Methyl-butyl)	Surital	H	$CH_2=CHCH_2$	$CH_3CH_2CH_2CH(CH_3)-$	"	"	
5-Allyl-5′-isobutyl	Sandoptal	H	$CH_2=CHCH_2$	$(CH_3)_2CHCH_2-$	"	"	0.2–0.4
5-(2-Bromoallyl)-5′-(1-methylbutyl)	Sigmodal	H	$CH_2=CBrCH_2$	$CH_3CH_2CH_2CH(CH_3)-$	"	"	0.1–0.2
5-Ethyl-5′-*sec.*-butyl	Butabarbital, Butisol	H	C_2H_5	$CH_3CH_2CH(CH_3)-$	"	"	
5-Isopropyl-5′-(2-bromoallyl)	Nostal	H	$(CH_3)_2CH$	$CH_2=CBrCH_2-$	"	"	
5-*sec*-Butyl-5′-(2-bromoallyl)	Pernoston	H	$CH_3CH_2CH(CH_3)-$	$CH_2=CBrCH_2-$	"	"	0.2
1-Methyl-5-isopropyl-5′-(2-bromoallyl)	Eunarcon	CH_3	$(CH_3)_2CH$	$CH_2=CBrCH_2-$			
1,5-Dimethyl-5′-cyclo-hexenyl	Evipal, Hexobarbital	CH_3	CH_3	CH_2 CH_2 $CH-$ $CH=CH$	1–4	0.25	0.25–0.4
5-Allyl-5′-(1-methyl-butyl)	Seconal	H	$CH_3CH_2CH_2CH(CH_3)-$	$CH_2=CHCH_2-$	"	"	0.1–0.2
2-Thio-5-ethyl-5′-(1-methylbutyl)	Pentothal, Thiopental	H(2-SH)	C_2H_5	$CH_3CH_2CH_2CH(CH_3)-$	"	"	Anesthetic
2-Thio-5-ethyl-5′-isoamyl	Thioethamyl	H(2-SH)	C_2H_5	$(CH_3)_2CHCH_2CH_2-$	"	"	Anesthetic
1-Methyl-5-ethyl-5′-phenyl	Prominal, Mebaral (IX-2)	CH_3	C_2H_5	C_6H_5-	"	"	
5-Isopropyl-5′-furfuryl	Dormovit	H	$(CH_3)_2CH$	α-C_4H_3O-			

TABLE II. SYNERGISTIC MIXTURES OF HYPNOTICS AND ANALGETICS

Trade name	Components
Veramon	Diethyl barbiturate + aminopyrine
Pyraminol	Phenobarbital and aminopyrine
Allonal	Allurate and aminopyrine
Lumalgin	Phenobarbital and Aspirin
Evicyl	Evipal and Aspirin
Cibalgen	Dial and aminopyrine

of different barbiturates are used by the public with or without prescription by physicians. Occasionally, intoxication by barbiturates has been observed, and a relatively large percentage of suicides has been traced to barbiturate poisoning. Approximately ten to fifteen times the usual hypnotic oral dose may become toxic. Death from barbiturates is due mainly to respiratory depression, sometimes complicated by pneumonia followed by vasomotor collapse, that is, various vessels no longer respond to stimulation. Relief from barbiturate poisoning symptoms may be obtained by artificial respiration and by stimulant analeptics such as caffeine, Coramine, Metrazol, picrotoxin, strychnine, and Benzedrine and other β-phenylisopropylamines.

In order to minimize the danger of poisoning if an overdose of barbiturates is taken with suicidal intent, a small amount of an emetic, such as ipecac, may be incorporated in an enterically coated pill. The amount of the emetic is so chosen that the ipecac will manifest its activity only if several times the therapeutic dose of the barbiturate has been ingested.

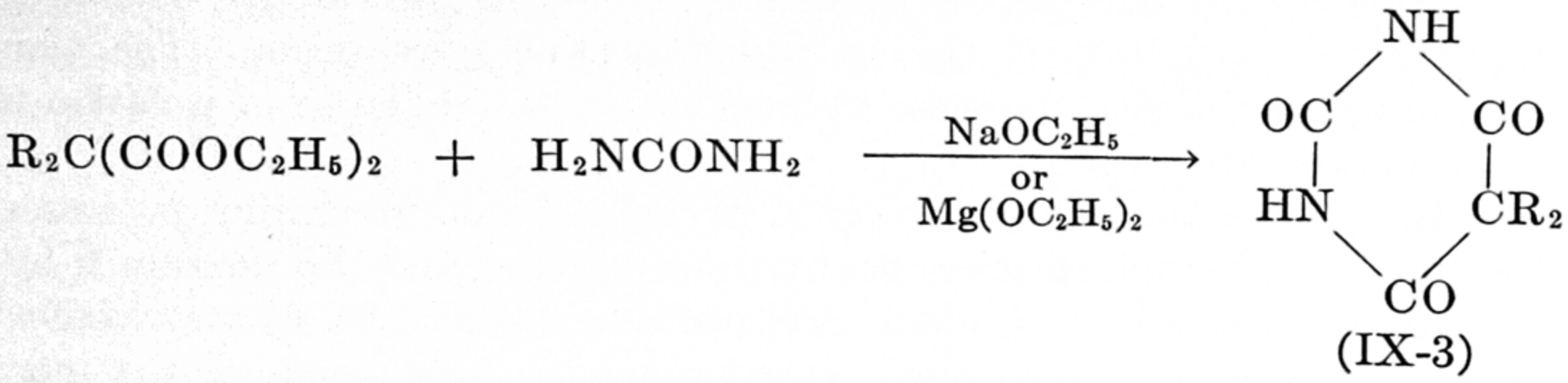
Prolonged use of barbiturates may lead to habituation. A craving for the drug is experienced when this is no longer administered. True addiction, however, as observed with opiates, and characterized by severe withdrawal symptoms is barely ever noticed in barbiturate habituation.

Counterindications to the use of barbiturates include: (*a*) allergic reactions caused by these drugs, (*b*) renal impairment, since several barbiturates are eliminated through the kidney, and (*c*) liver disease because a number of them are oxidized and detoxicated in the liver. In patients with liver disease, non-toxic doses of barbiturates may produce profound and unduly prolonged sleep. On the whole, the rate of detoxication in the liver is sufficient to minimize the danger of cumulative toxicity.

2. Synthesis of Barbituric Acids

The synthesis of 5,5′-disubstituted barbiturates (IX-3) has not been changed much during the last forty years. They are manufactured by condensing disubstituted esters of malonic acid with urea in the presence of

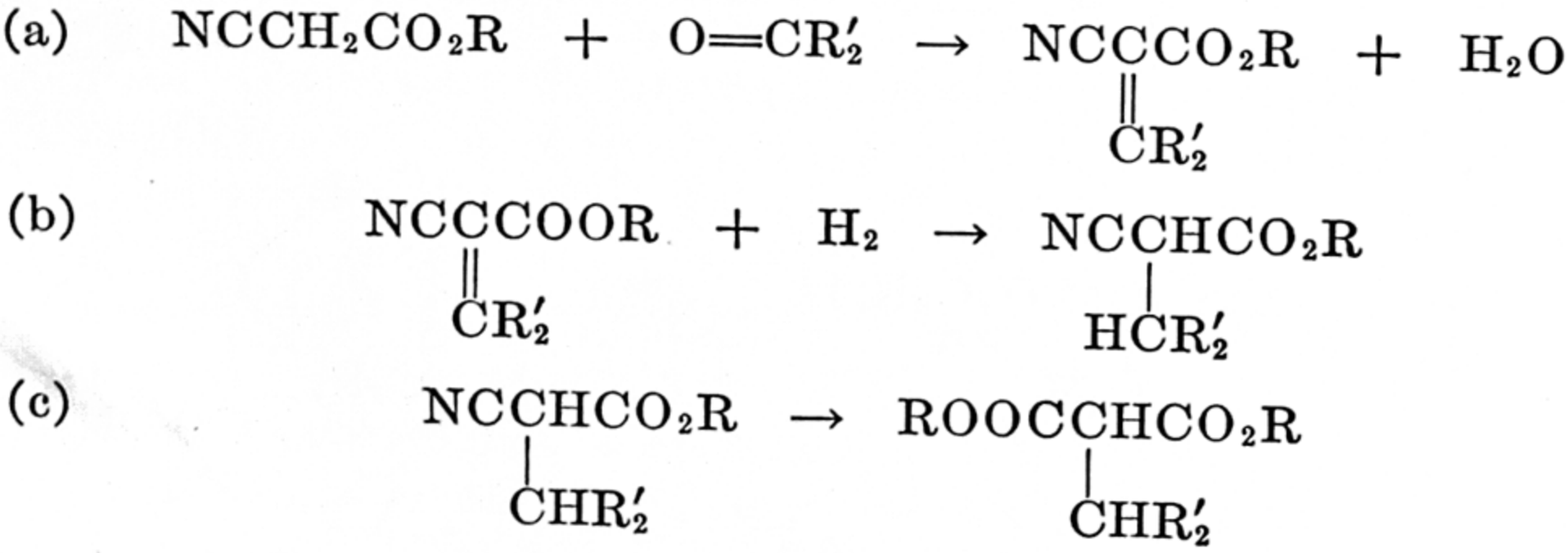
sodium methoxide or ethoxide. Only in the case of very active alkyl halides such as allyl, or benzyl halides is it possible to substitute barbituric acid directly with these alkyl groups.



(IX-3)

With the introduction of unsymmetrically substituted 5,5′-dialkyl barbituric acids[3] it became increasingly important to improve the yield of the monoalkylmalonate ester first obtained into which another radical is to be introduced later. In almost all cases the alkylation of malonic ester leads to a mixture of mono- and dialkyl derivatives in which some of the unsubstituted ester is left over. In the case of the smaller alkyl groups such as methyl it is difficult to separate these materials by fractional distillation, or even by the differences between their solubility in dilute alkali. The malonates retaining at least one acidic hydrogen at the carbanion position are somewhat soluble in ammonium hydroxide and similar weak bases but this property depends too much on the character of the substituent to permit clean-cut separation from disubstituted malonic esters. If the two alkyl groups have a considerable weight such as two amyl groups, two heterocyclic groups etc., fractionation becomes easier because the dialkyl derivatives with large alkyl groups show a much higher boiling point than the monoalkyl derivatives.

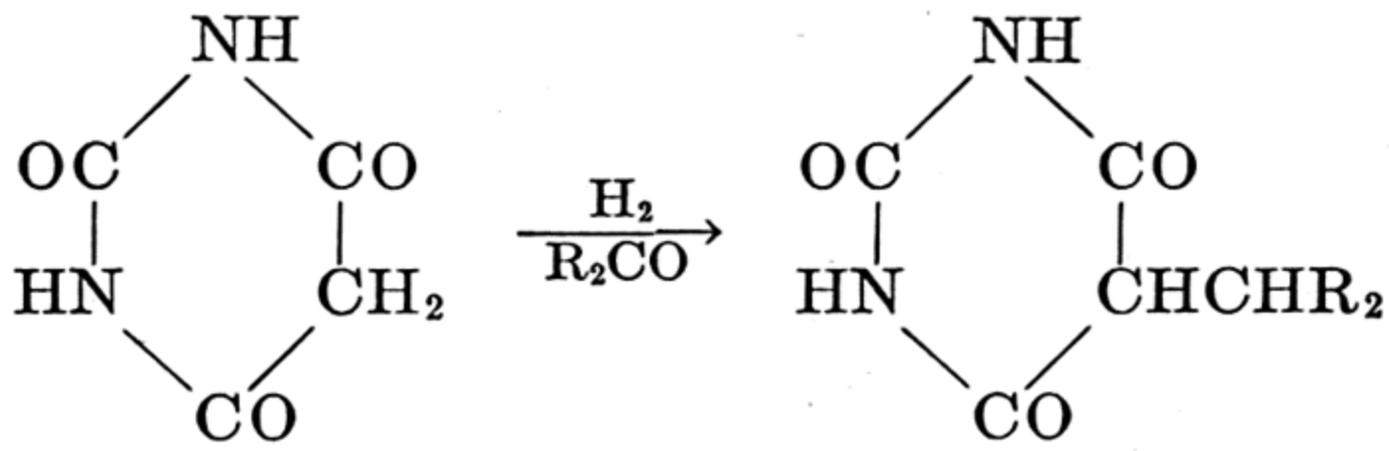
To meet the difficulty of getting pure monalkyl malonic acids two methods have recently been proposed. In one of them[4] alkyl cyano-



[3] Shonle and Moment, *J. Am. Chem. Soc.*, **45**, 243 (1923).
[4] Alexander and Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).

acetates are reduced catalytically in the presence of aliphatic carbonyl compounds. Alkyl cyanoalkylacetates (NCCHR'COOR) which may then be hydrolyzed to monoalkyl malonic acids are obtained in this process. The unsaturated derivatives formed by equation (a) can be isolated in many cases, and support the proposed reaction mechanism. The main advantage of the simultaneous hydrogenation is avoidance of isolation of these unsaturated intermediates.

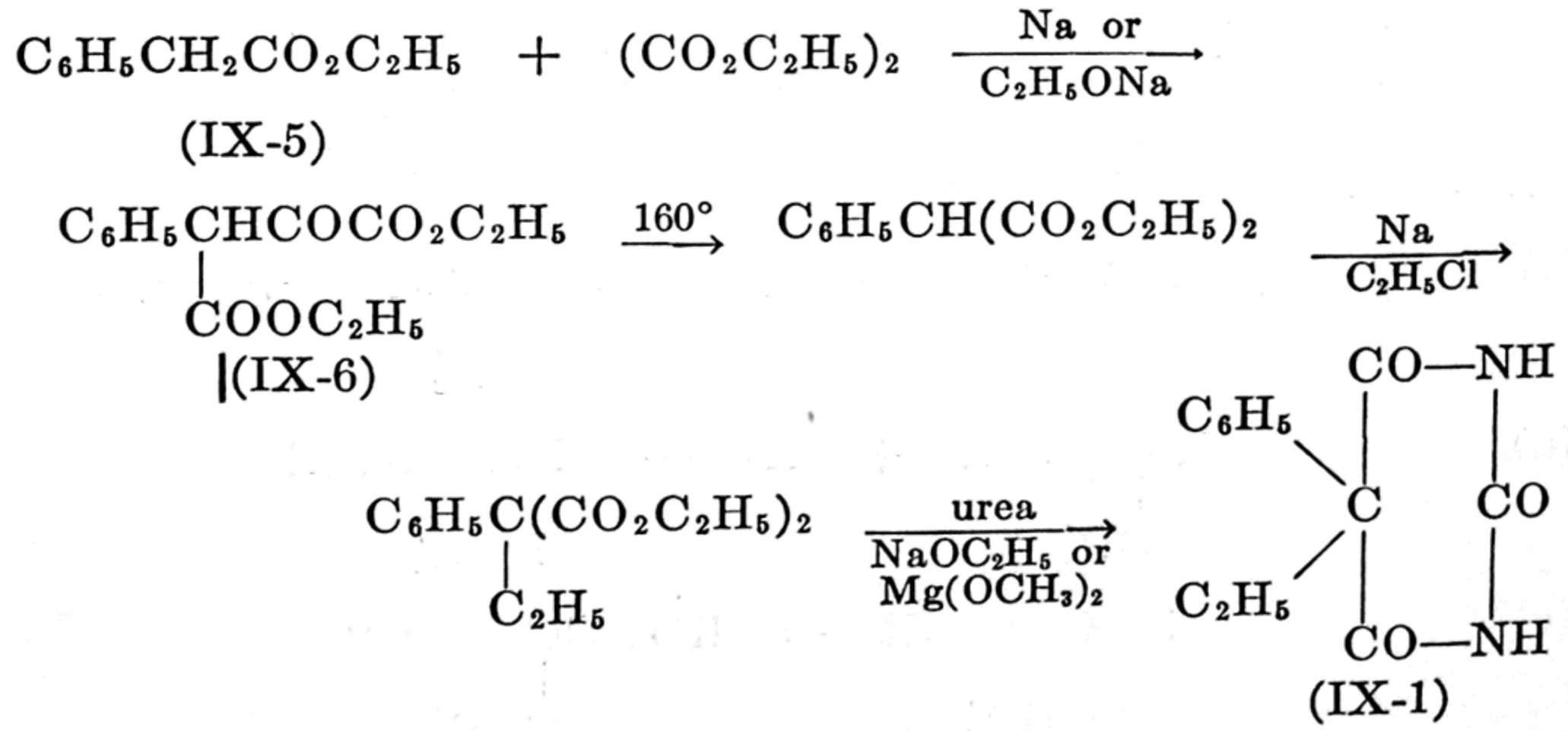
In another route particularly applicable to manufacturing processes[5] barbituric acid is mixed with aldehydes or ketones and the mixture is hydrogenated. In all cases, monoalkyl barbituric acids (IX-4) are obtained from this reaction. Into these compounds, at least some of the more reactive alkyl groups such as allyl or benzyl, may be introduced to yield the corresponding dialkyl barbiturates.



(IX-4)

(one R may be H)

It is not possible to substitute aryl groups into diethyl malonate, and the synthesis of the important drug phenobarbital (IX-1) has to take this factor into account. The chief task here is the preparation of diethyl



(IX-1)

[5] Wenner, in *Jubilee Volume Emil Barell*. Reinhardt, Basle, 1946, p. 435.

phenylmalonate which may be achieved, for instance, by condensing ethyl phenylacetate (IX-5) with ethyl oxalate, and decarbonylating the resulting α-keto ester (IX-6) by heating, sometimes with the aid of powdered soft glass. Alkylation of the remaining active hydrogen and condensation with urea under the influence of sodium or magnesium alkoxide complete the synthesis.

3. Relation of Structure and Activity

The monoalkyl and monoaryl derivatives of barbituric acid are physiologically almost inactive. The same holds for barbituric acids sub-

TABLE III. Relative Activity of 10% Solutions of Sodium Salts of Barbituric Acids in Rabbits[3]

Derivative of barbituric acid	Mol. wt.	Inability to rise when shaken, g./kg.	Toxic dose g./kg.	Therapeutic Index	Remarks
Dimethyl	156	—	—	—	
Diethyl	184	0.15	0.25	1:1.7	
Dipropyl	212	0.06	0.22	1:3.7	
Propyl-isopropyl	212	0.05	0.15	1:3	
Di-*n*-butyl	240	0.35	0.50	1:1.4	Dizziness
Dibenzyl	308	—	—	—	
Ethyl-isopropyl	198	0.10	0.20	1:2	
Ethyl-isobutyl	212	0.05	0.12	1:2.4	
Ethyl-*n*-butyl	212	0.04	0.10	1:2.5	
Ethyl-*sec*-butyl	212	0.05+	0.20−	—	
Ethyl-isoamyl	226	0.04	0.17	1:4.2	
Propyl-isoamyl	240	0.08	0.22	1:2.8	
Ethyl-benzyl	246	0.04	0.06	1:1.5	Convulsions
Benzyl-isopropyl	260	0.20	0.35	1:1.8	
Benzyl-propyl	260	0.20	0.45	1:2.3	Convulsions
Ethyl-phenyl	232	0.08	0.15	1:1.9	

stituted in the 5-position with two very small alkyl groups. Dimethyl barbituric acid is without apparent action on rabbits in a dose of 0.75 g./kg. As the molecular weight is increased the activity mounts until a maximum is reached. When the sum of the carbon atoms in the groups at position 5 is larger than seven or eight, the hypnotic activity drops and the animal under observation only shows muscular incoordination or no effect at all as is the case in dibenzyl barbituric acid.[6] This particular compound was of interest in view of the discovery by Macht that benzyl alcohol possesses antispasmodic and relaxing properties. The inactivity

[6] Dox and Yoder, *J. Am. Chem. Soc.*, **44,** 1141 (1922).

of dibenzyl barbituric acid is an example for the old experience in medicinal chemistry that incorporation of two active groups in one compound usually abolishes effectiveness.

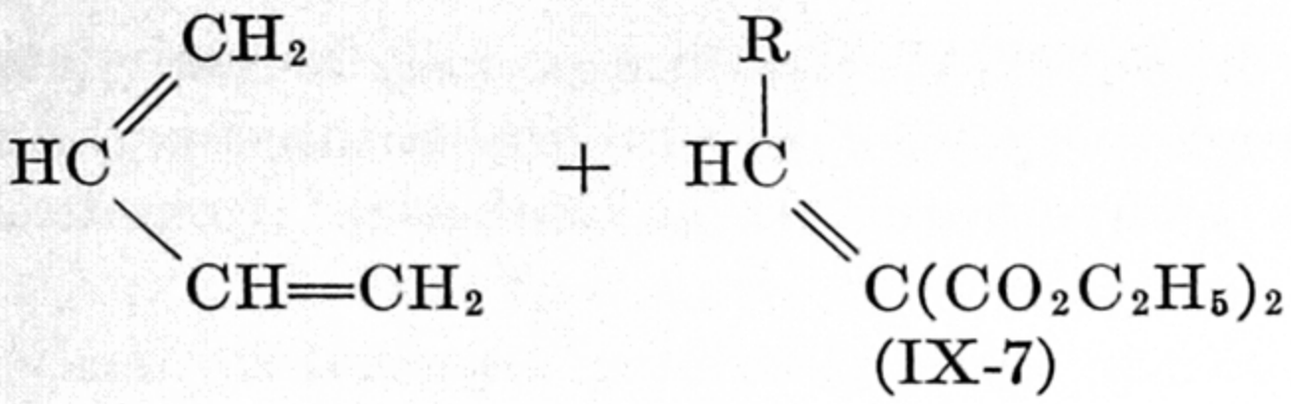
It may be stated that branched chain aliphatic groups are more active and less toxic than the straight chain ones. Table III lists the relative activity of 10% solutions of sodium salts of certain barbituric acids in rabbits.

The optimum relation between therapeutic activity and toxic dose is reached in the series of substituted barbituric acids in the case of isoamyl-ethyl barbituric acid (Amytal). For many barbituric acids the ratio of toxic to therapeutic dose is approximately the same although there are exceptions to this rule. For instance, 0.15 g./kg. of sodium diethyl barbiturate puts a rabbit to sleep while 0.25 g./kg. produces death. In contrast, 0.04 g./kg. of isoamyl-ethyl barbituric acid is hypnotic in rabbits; a slightly larger dose of 0.0404 gram produces extremely deep sleep while not less than 0.15 g./kg. kills 50% of the animals.

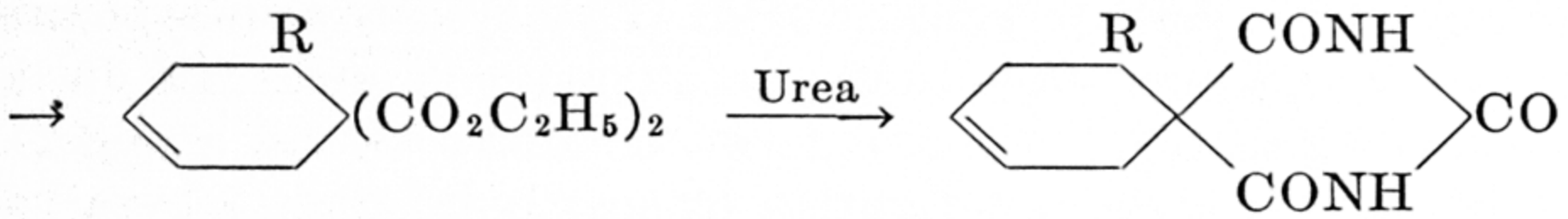
The dialkyl barbituric acids show marked differences in hypnotic action depending on the nature of the alkyl groups in position-5. It was thought that a hint as to the usefulness of certain alkyl groups in this position might be obtained by studying the effect of variations in the alkyl radicals on the hypnotic activity of simple or substituted alcohols. In general, lengthening of the alkyl chain leads towards a more favorable lipid solubility and therefore greater hypnotic power. However, the regularities found in alcohols, that primary alcohols are more active than secondary alcohols, or that branched primary alkyl groups are more active than normal alkyl groups do not hold well in the barbituric acid series. Introduction of polar or functional groups into the alkyl groups such as ether or keto groups, hydroxyl, carbonyl, amino or carboxyl groups usually destroys the depressant effect. It may be that these groups lessen the tendency of the alkyl groups to impart lipid solubility to the molecule.

High therapeutic ratios between narcotic and toxic doses are observed in a series of spirobarbiturates.[7] They are prepared by a diene synthesis from diethyl alkylidenemalonates (IX-7). Hydrogenation of the alkyl-substituted ethyl cyclohexenemalonates (IX-8) first obtained produces the corresponding saturated derivatives (IX-9), and condensation of either ester with urea furnishes the two series of 5,5-spirobarbiturates (IX-10 and 11). The *n*- and isopropyl derivatives in both series possess the most favorable properties.

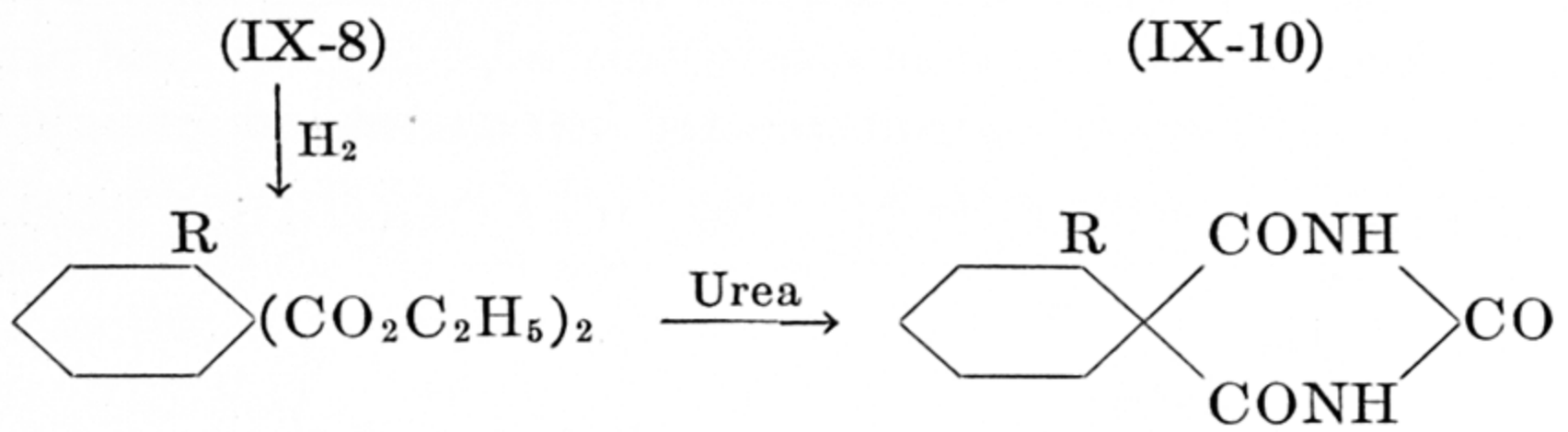
[7] Cope, Kovacic and Burg, *J. Am. Chem. Soc.*, **71**, 3658 (1949).



(IX-7)

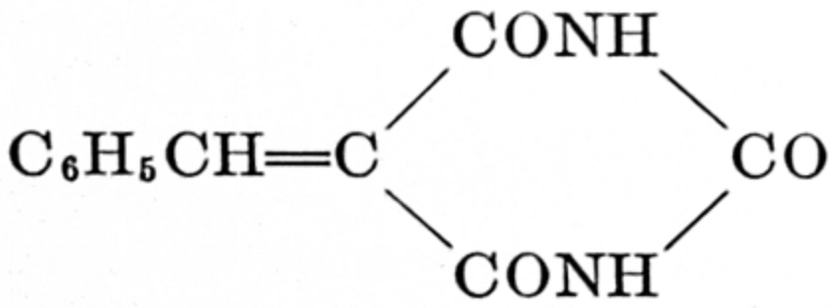


(IX-8) (IX-10)

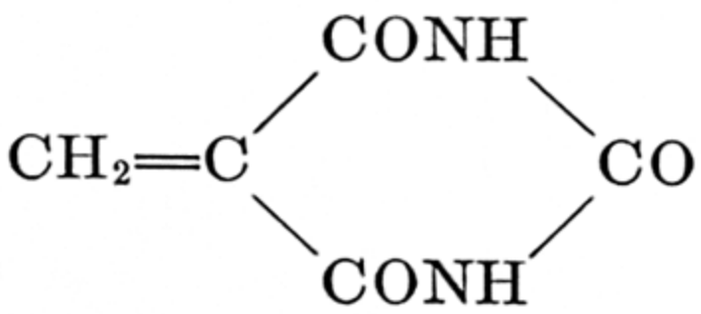


(XI-9) (XI-11)

These compounds are an exception to the rule that replacement of both valences at C_5 by one group gives inert compounds. For example, 5-benzalbarbituric acid (IX-12) and 5-methylenebarbituric acid (IX-13) are inactive.



(IX-12)



(IX-13)

This holds also for the introduction of two small, or certain large like groups, two methyl, two benzyl, or two amide groups. Only if the total molecular weight amounts to approximately 250, and the sum of the carbon atoms in the two alkyl groups is around seven or eight will two like alkyl groups be satisfactory in producing hypnotic activity. In order to account for the differences in activity of a number of primary and secondary groups such as the *n*-amyl and the secondary amyl, or the *n*-butyl and the secondary butyl group, it has been claimed that groups which contain asymmetric carbon atoms have increased activity. However, the synthesis of some optically active barbituric acids with asymmetric centers in the alkyl groups has not borne out this prediction.

If one of the alkyl groups at C_5 is very reactive as in benzyl or propargyl ($CH_2C{\equiv}CH$) groups, the resultant barbituric acid often has anti-

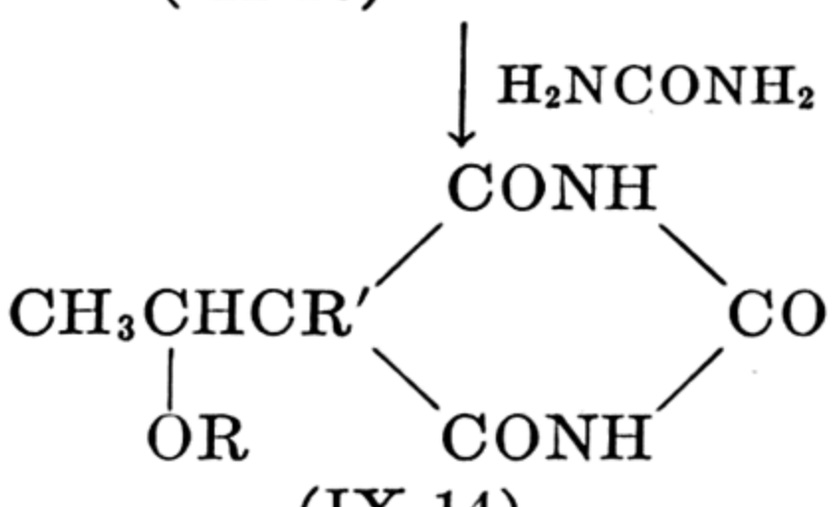
convulsant activity at lower doses. N-Alkylation, especially N-methylation, seems to confer anticonvulsant properties on 5,5-disubstituted barbituric acids. Mebaral (IX-2) is such a case. It is synthesized from diethyl phenyl-ethylmalonate and methylurea.

Among the dialkylbarbituric acids containing oxygenated functions, certain α-alkoxyethylbarbituric acids (IX-14) have shown promising properties. Synthesized from α-alkoxyvinylmalonic esters (IX-15) and subsequent condensation with urea,[8] two members of this group (IX-17 and IX-18) caused a shorter duration of anesthesia than Amytal, and had a more favorable therapeutic ratio (Amytal, 2.22). These properties should make these compounds suitable for intravenous anesthetic purposes.

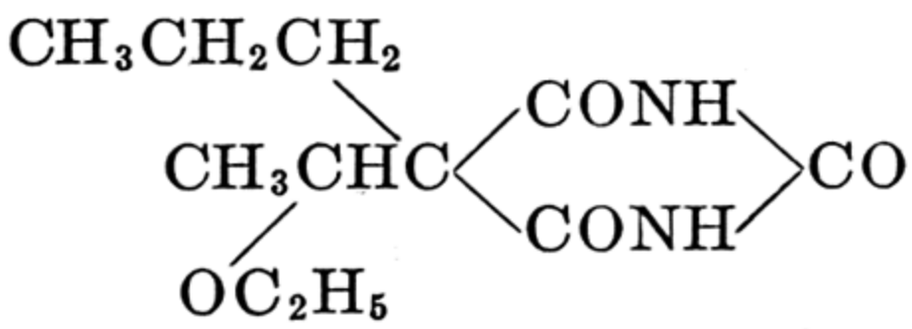
$$CH_2{=}C(OR)CR'(CO_2C_2H_5)_2 \xrightarrow{H_2} CH_3CH(OR)CR'(CO_2C_2H_5)_2$$

(IX-15)

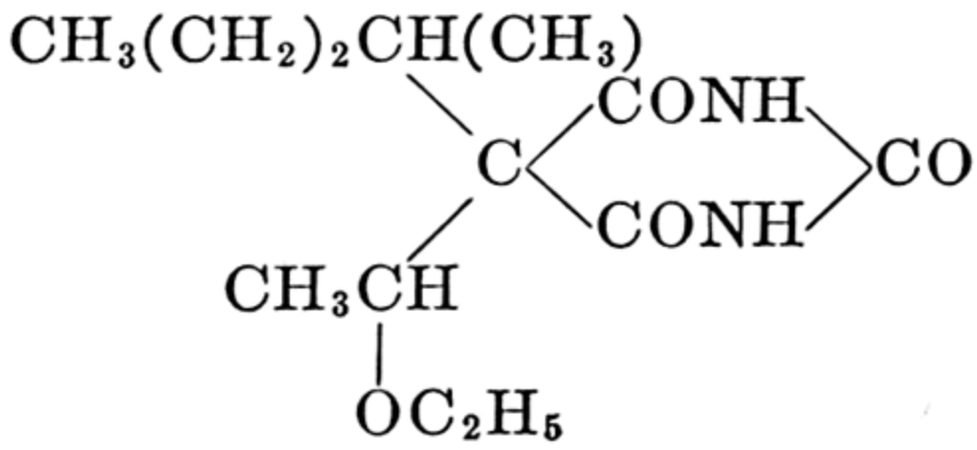
(IX-16)



(IX-14)



(IX-17)
Therapeutic ratio: 3.75



(IX-18)
Therapeutic ratio: 2.67

All serious attempts to correlate the results of substituting various alkyl groups with changes in the activity of the resulting compounds have remained erratic. The problem has been reviewed systematically by Shonle.[9]

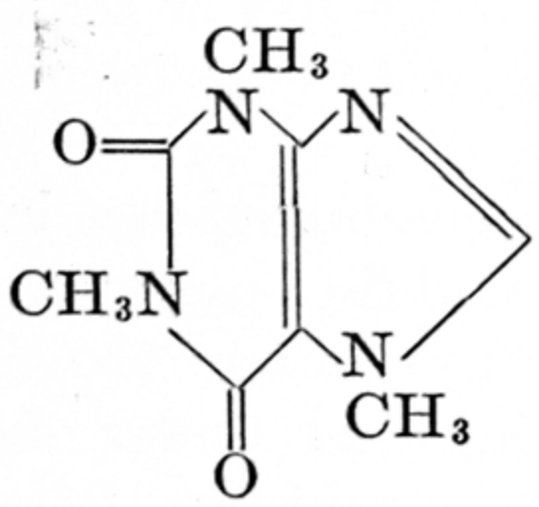
4. Effect of Chemical and Physical Properties

As in all other groups of drugs, a combination of physical and chemical properties plays an important role in determining the physiological characteristics of the barbituric acids. Like other depressant agents these

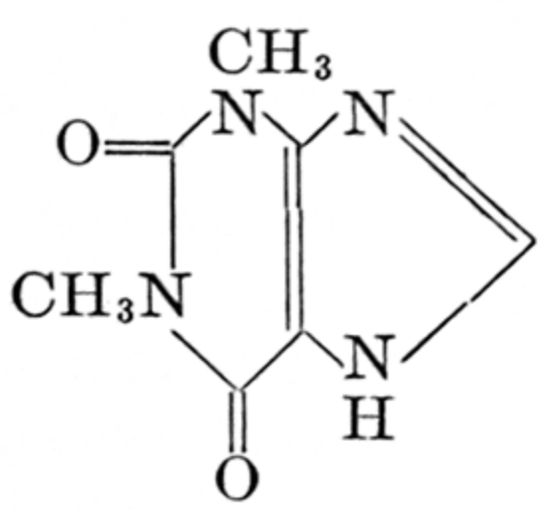
[8] McElvain and Burkett, *J. Am. Chem. Soc.*, **64**, 1831 (1942).
[9] Shonle, *J. Ind. Eng. Chem.*, **23**, 1104 (1931).

compounds must consist of lipotropic alkyl radicals attached to a hydrotropic polar group (the trioxypyrimidine moiety) which is capable of forming associated molecules in polar solvents and which may possess similarity to compounds occurring in the body. The latter property is not essential, but it is interesting to speculate about the relation of the barbiturates to the isoalloxazines, nucleic acids, thiamine and similar compounds containing pyrimidine rings.

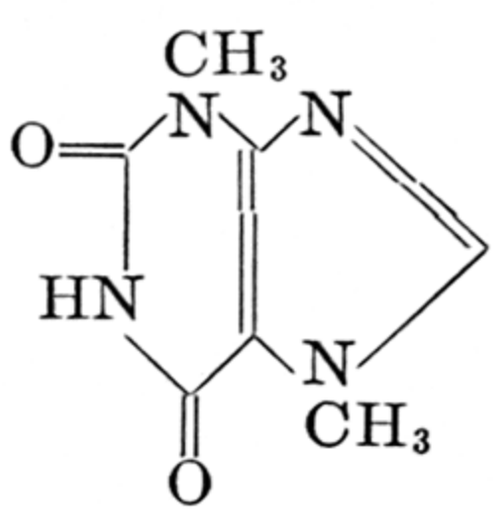
An analogy appears to exist between the structures of the hypnotic barbiturates, and those of the cerebral stimulants among the purine alkaloids. Caffeine (IX-19) stimulates only the cerebral cortex in small doses; minor modifications of its structure as they are seen in theophylline (IX-20) and theobromine (IX-21) decrease or abolish this property. It is believed that the depressant effect of the barbiturates is antagonistic to the analeptic action of caffeine.



(IX-19)



(IX-20)



(IX-21)

On the whole, all hypnotics are expected to exhibit a certain chemical stability in order to permit sufficiently long duration of action. Some biological degradation is necessary but, like the anesthetics, the hypnotics must not be destroyed too rapidly in the body. If chemical changes do not occur at all, depressant activity will barely ever be noticed. Shonle and Moment[3] have demonstrated approximate ratios of *in vivo* degradation for certain barbiturates substituted by saturated alkyl groups. When injected subcutaneously into dogs, about 90% is recovered unchanged in the urine while only 62% is found unchanged after oral administration. The metabolic fate of barbiturates will be discussed below.

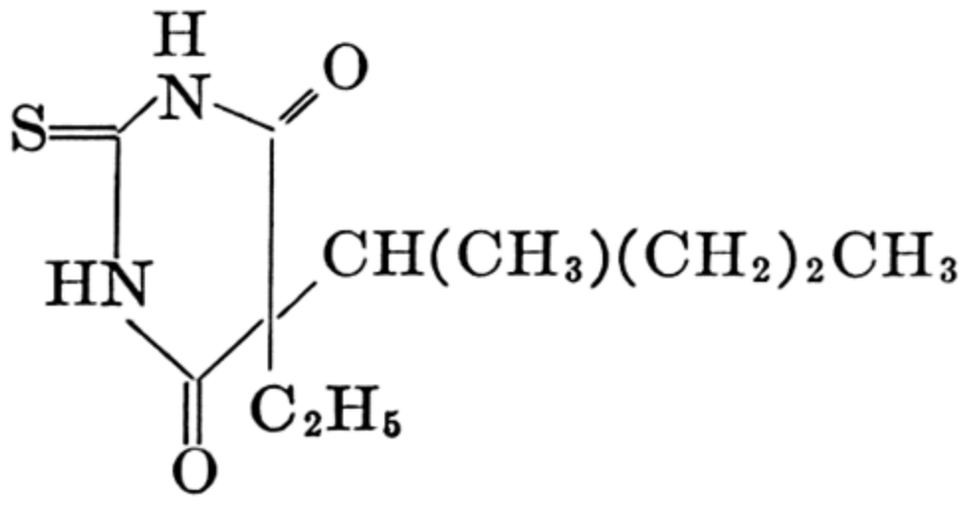
The barbituric acids are very weakly acidic, and the body liquids must have a decisive and not yet understood effect on the pH of the hypnotics. Various investigators have tried to correlate hypnotic activity with certain individual physical properties of the barbiturates; thus, the water solubility of *sec*-amylethylbarbituric acid is twice that of the more active isoamyl-ethyl isomer, and the latter has the higher partition coefficient between oil and water. In other cases, the ability of certain barbiturates to depress surface tension has been measured, but as in the series of anesthetics these experiments have not disclosed definite regularities. It has

been suggested that the pH of the barbituric acids influences the rapidity of the onset of their action, but while this factor may be utilized in planning the preparation of rapidly acting hypnotics, it does not account for the duration of the sleep produced.

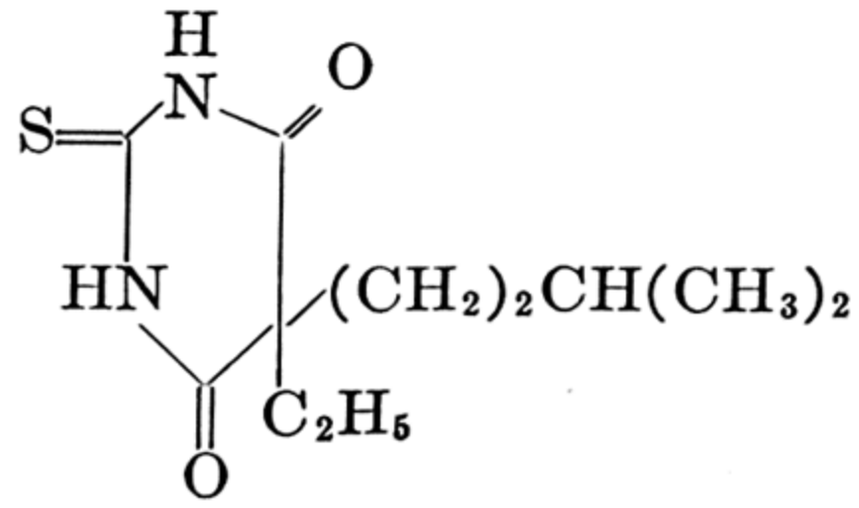
The complexity of evaluating such one-factor tests may be gathered from a comparison of diallyl barbituric acid (Dial) and allyl-(1-methylbutyl) barbituric acid (Seconal). In both drugs, the allyl groups promote reactivity, and therefore acidity of the respective molecules, and both compounds bring about speedy hypnosis. It might be expected that the more unsaturated of the two drugs (Dial) should be more easily destroyed by oxidative cleavage and thereby be the shorter-lasting member of the pair. Actually, the reverse is true: Seconal maintains sleep for not much over four hours while the same dose of Dial can keep a patient asleep for as long as eight hours. It is obvious that other factors, not yet measured, influence duration of hypnosis.

5. Thiobarbiturates

Certain 5,5′-dialkyl-2-thiobarbiturates have been introduced in recent years as intravenous anesthetics. Especially 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid (Pentothal, IX-22) and 5-ethyl-5-isoamyl-2-thiobarbituric acid (Thioethamyl)[10, 11] (IX-23) when injected under carefully prescribed conditions, produce surgical anesthesia rapidly. The anesthesia is of short duration and leaves no ill after-effects. These compounds are also used in block anesthesia, particularly to anesthetize selected regions of the body by injection into the spinal fluid.



(IX-22)



(IX-23)

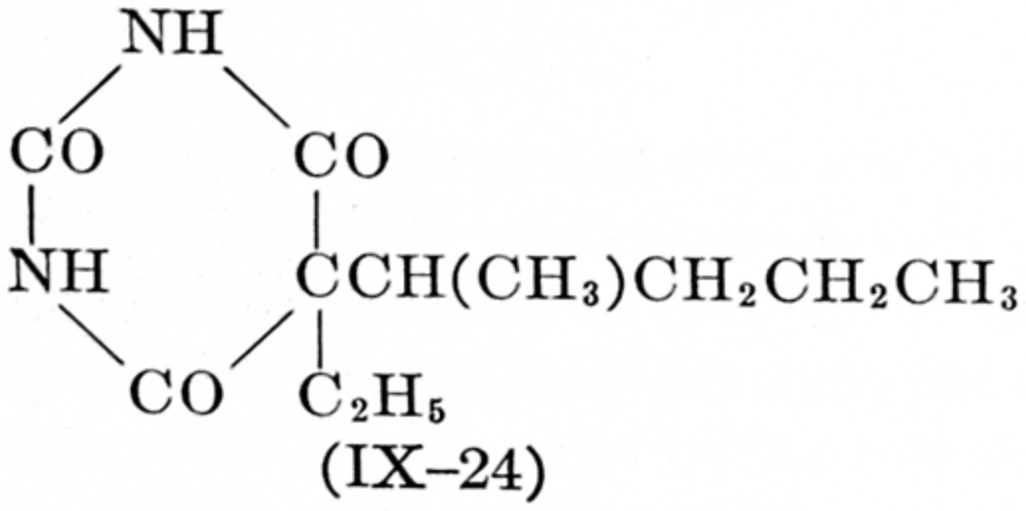
The synthesis of the thiobarbiturates follows the same general route as that of their oxygen analogs, namely, condensation of dialkyl substituted malonic esters with thiourea. As shown by acidimetric titrations, thiobarbiturates are more acidic than the corresponding barbiturates, and this property may, perhaps, account for the rapid onset of their action.

[10] Tabern and Volwiler, *J. Am. Chem. Soc.*, **57,** 1961 (1935); **58,** 1355 (1936).
[11] Miller, Munch, Crossley, and Hartung, *J. Am. Chem. Soc.*, **58,** 1090 (1936).

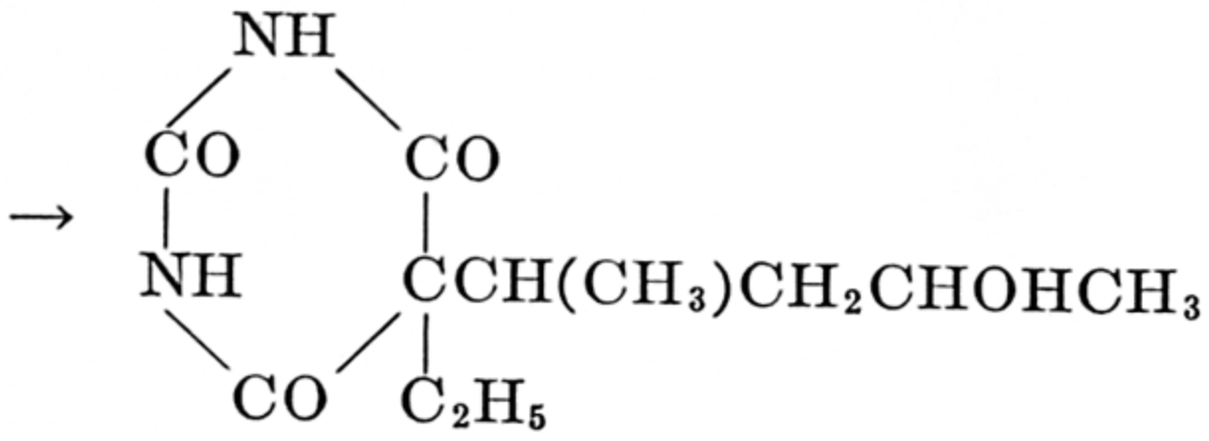
A very effective thiobarbiturate for intravenous anesthesia of dogs and rats has recently been found in Thionarcon (5-ethyl-5′-(butylthiomethylene)-2-thiobarbituric acid.[12]

6. Metabolism of Barbiturates

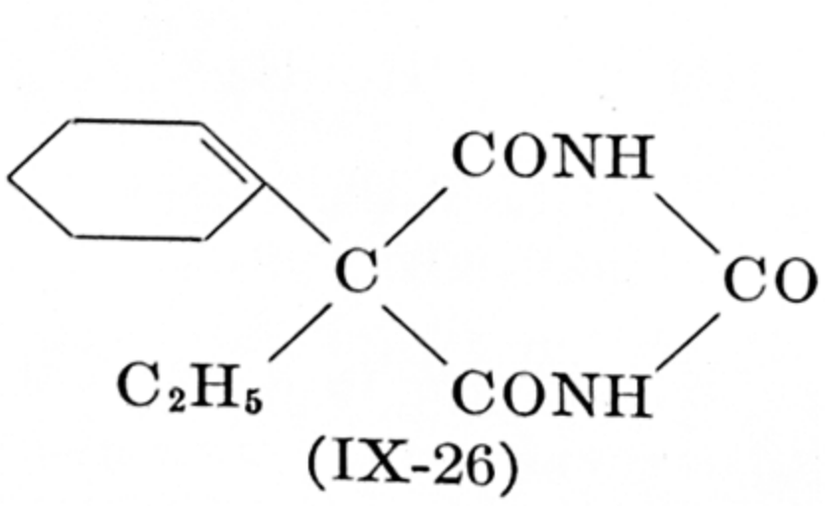
The metabolic fate of barbiturate hypnotics has a profound influence on the duration and intensity of their action. As may be expected, the more rapid their rate of excretion, the shorter the duration of action of the drugs. Rate of excretion does not appear to be directly related to metabolic alteration, as far as the meager available information permits to conclude. Diethyl barbiturate is excreted without change in the urine, as are also considerable amounts of phenobarbital, Dial, Rutonal and Allonal. Other useful barbiturates are metabolized in the liver almost entirely before being excreted. The N-methyl barbiturates, such as Prominal, are demethylated in the organism; the nor-compounds can be isolated, and since they are ordinarily less active than the N-methyl derivatives, deactivation appears to halt at a stage of decreased rather than entirely lost activity. It would therefore be imprudent to attribute the deactivation of N-methyl compounds to dealkylation. This conclusion is similar to that reached



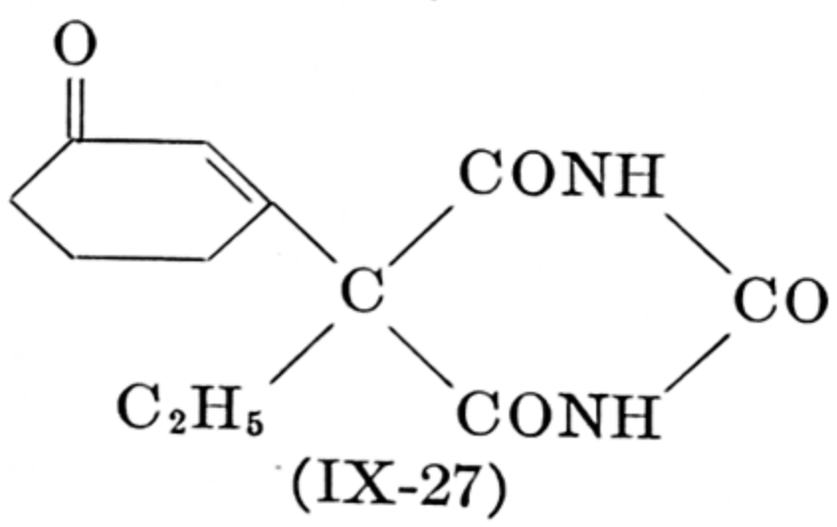
(IX–24)



(IX–25)



(IX-26)



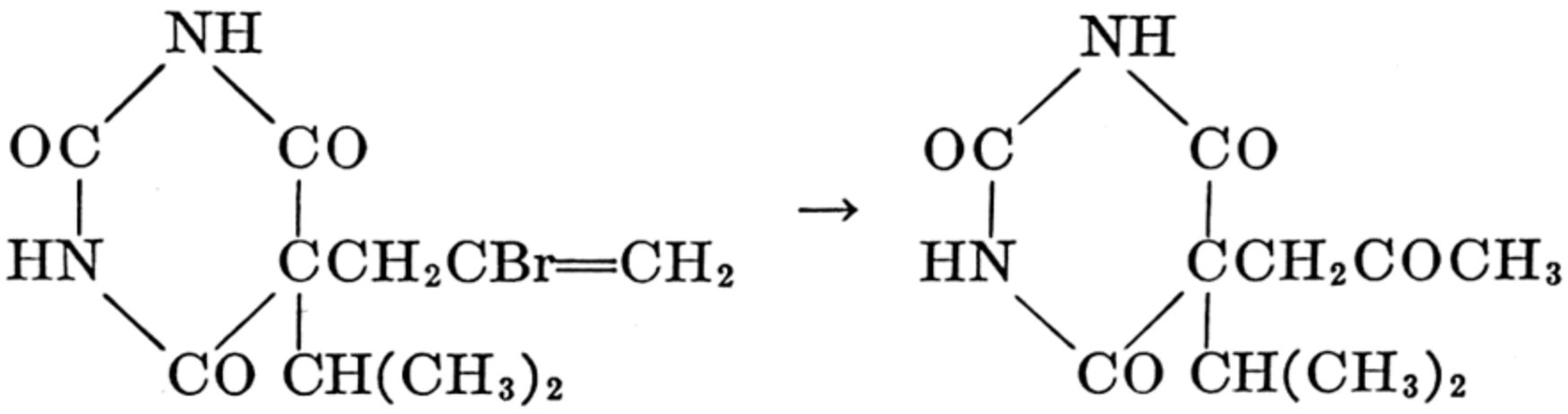
(IX-27)

[12] Zuccari, *Pharm. Prod.*, **4**, 532 (1949).

for the relation of the metabolic demethylation of caffeine to the analeptic action of this alkaloid (Chapter XII).

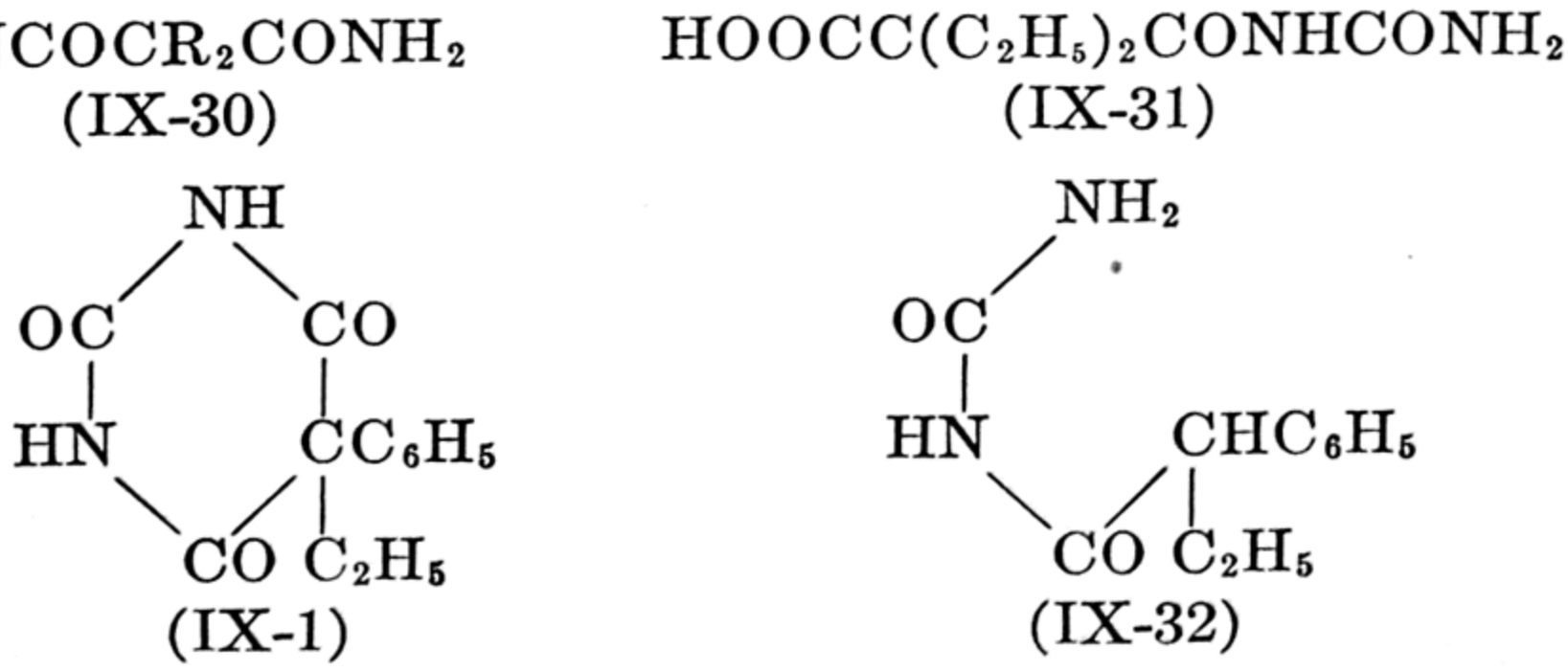
Barbiturates substituted by branched alkyl, or by aliphatic or cyclic alkenyl groups in position 5, are oxidized, principally in the liver. Examples are the fate of Pentobarbital (IX-24) which is oxidized to the alcoholic barbiturate (IX-25); and that of Phanodorn (IX-26) which is metabolized to the α,β-unsaturated ketone (IX-27). The metabolic product (IX-25) is excreted as the dextrorotatory form; the latter is pharmacologically inactive even in large doses.[13] This appears to be a true case of detoxication.

Barbiturates containing the 2-bromoallyl group undergo hydrolysis of the bromine to yield acetonyl derivatives (IX-29). The fate of Pernoston (IX-28) illustrates this reaction.



(IX-28) (IX-29)

It might be assumed that the most sensitive linkages in the barbituric acid molecules, the amide or ureide groups, should be the first points of biological hydrolytic attack. Amides or ureides of disubstituted malonic acids would result from such reactions, and the possibility could not be overlooked that these compounds are the actual hypnotics. When, however, diethyl- and dipropylmalonamide (IX-30) and the ureide of the diethylmalonic acid (IX-31) were tested, no hypnotic activity was



(IX-30) (IX-31)

(IX-1) (IX-32)

detected. There is actually no experimental evidence to show that the barbiturates are hydrolyzed to either amides or ureides of the corresponding

[13] Maynert and Van Dyke, *Science*, **110**, 661 (1949).

malonic acids before they reach the brain cells. This is surprising in view of the observation that similar acylureas related to barbiturates have shown pronounced and useful anticonvulsant activity. Thus (2-phenylbutyryl) urea (IX-32) related to phenobarbital (IX-1) counteracts efficiently convulsions brought about by electroshock (see Chapter X).

The metabolism of barbiturates has recently been reviewed in detail.[14]

IV. ALCOHOLS AS HYPNOTICS

Ethyl alcohol has been used as a sedative and hypnotic ever since man learned to produce it by fermentation of grains. It causes, like all other depressant agents of the central nervous system, a state of excitement before depression sets in, and man has derived more pleasure from this property of ethanol than from the sleep that follows the excitement. In view of the fact that alcoholic liquors can be purchased universally without a physician's prescription, self-medication for lack of sleep probably makes more use of alcohol than of any other drug. As a rational therapeutic, however, it has long been superseded by less toxic hypnotics, particularly because of the danger of chronic alcoholism involved in its continued use.

Richardson[15] observed as early as 1869 that hypnotic activity of alcohols increases with the molecular weight. A maximum is reached in *n*-hexanol or *n*-octanol; the activity curve declines with a further lengthening of the alkyl chains and disappears in hexadecanols (see Chapter III). Branching of the alkyl chain raises activity, and so does the transition from primary through secondary to tertiary alcohols in an isomeric series. Besides ethanol, tertiary amyl alcohol (2-methyl-2-butanol) is the only simple alcohol which has found practical use. It is employed now only as a synergistic solvent for tribromoethanol (see below) because it increases the depth and duration of the sleep produced by this drug.

A more favorable distribution coefficient between lipids and aqueous body liquids is attained by chlorinating or brominating simple branched or unbranched alcohols. Both trichloro and tribromoethanol are powerful hypnotics. The latter, dissolved in *tert*-amyl alcohol, is used as "Avertin (with Amylene Hydrate)" for basal and general anesthesia as described in Chapter VII.

Trichloroethanol, although causing less respiratory depression, has certain excitatory side-effects and will probably not be used as such. There is little doubt, however, that it is the active stage to which the corresponding aldehyde, chloral, is reduced in the organism: trichloroethanol is found in the urine of animals treated with chloral.

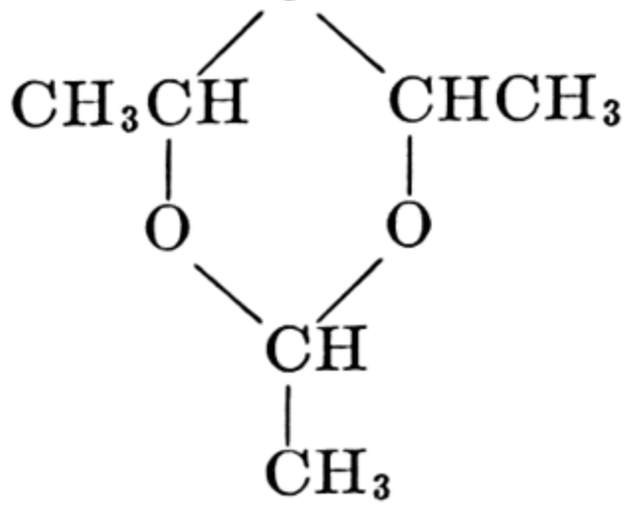
[14] Maynert and Van Dyke, *J. Pharmacol. Exptl. Therap.*, **96,** 217 (1949).
[15] Richardson, *Med. Times and Gaz.*, **18,** 703 (1869).

Trichloroisopropyl alcohol (Isopral, $Cl_3CCHOHCH_3$) is more active than chloral but too toxic for general use. 1,1,1-Trichloro-2-methyl-2-propanol (Chloretone, Chlorobutanol) also is a powerful hypnotic and is used occasionally for preanesthetic sedation. It is widely applied to produce long-lasting anesthesia in laboratory animals, and because of its low toxicity and pronounced bacteriostatic and anesthetic properties has been recommended for pharmaceutical preparations in the treatment of nasal irritations.

V. ALDEHYDES AND KETONES

It is not certain whether simple aliphatic aldehydes exert their slow hypnotic effect by being reduced to the corresponding alcohols, but their toxic manifestations have made even this fundamental study unattractive. The depressant effect of aromatic aldehydes is questionable. On the other hand, acetophenone has been used as a hypnotic under the name of Hypnon but has become obsolete by the discovery of safer drugs with a wide choice of graded activity.

The trimer of acetaldehyde, paraldehyde (IX-33) may be regarded as a cyclic acetal of the parent compound. It acts similar to ethyl alcohol.



(IX-33)

Its most distinguishing disadvantage is its pungent odor and taste and its irritating effect upon mucous membranes. The breath exhaled by individuals asleep under the influence of paraldehyde imparts to the surroundings so strong an odor of fusel oils that hospital attendants have been known to refuse to enter rooms of such patients. Nevertheless, the promptness of its action has preserved paraldehyde a valuable place in psychiatric practice. A search for hypnotic activity in similar cyclic trimeric aldehydes has failed to yield additional drugs in this series.

As with the alcohols, halogenation and particularly chlorination creates a set of physical properties conducive to hypnosis. The best-known example in this group is chloral which, for the sake of convenience, is usually marketed as the crystalline stable and water-soluble hydrate,

$Cl_3CCH(OH)_2$. Its introduction into therapy was based on false premises and provides one of the classical stories of medicinal chemistry, repeated in other cases with due variants.

Chloroform was known as an anesthetic, and its formation from chloral by the haloform reaction permitted the conclusion that administration of chloral would result in a slow release of the active chloroform. Therapeutic trials confirmed the prediction of the depressant activity of chloral, and the aldehyde enjoyed great popularity for many years in simple insomnias which it tends to relieve efficiently. Only after the introduction of the barbiturates did chloral hydrate begin to lose ground, since its irritating effect on the stomach and its depressant effect on heart and respiration could not measure up to the newer, less toxic drugs.

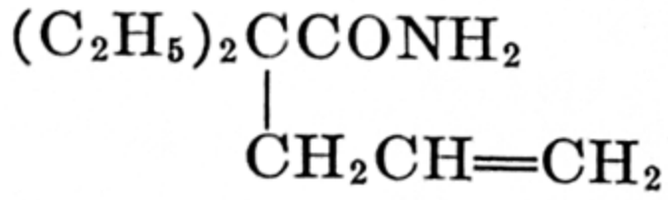
The path of the physiological action of chloral, however, had been interpreted erroneously. No evidence of a "physiological haloform cleavage" has been obtained, and chloroform is certainly not the product to which the action of chloral can be attributed. When chloral is fed to dogs, it is reduced to trichloroethanol which can be recovered from the urine as the glucuronate. It is noteworthy that bromal shows no hypnotic action[16] while its reduction product, tribromoethanol, is an excellent narcotic.

VI. AMIDES, UREAS, AND BIURETS AS HYPNOTICS

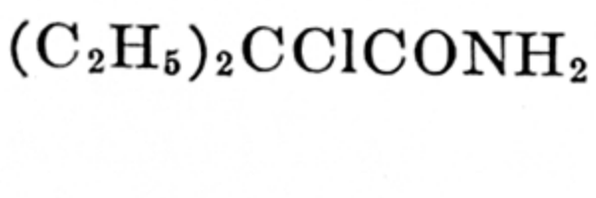
No useful hypnotic drugs have been found in this group of compounds but several members of these series combine sufficient centrally depressant properties with a lack of undesirable side effects to act as sedatives. They often have mild analgetic activity. They may influence favorably hysterical conditions, excited states due to mental disorders, simple nervous insomnias, and neurotic acceleration of the heart.

N,N-Diethylisovaleramide, $(CH_3)_2CHCH_2CON(C_2H_5)_2$, which has been marketed under the name Valyl, is a typical representative of a simple sedative amide.

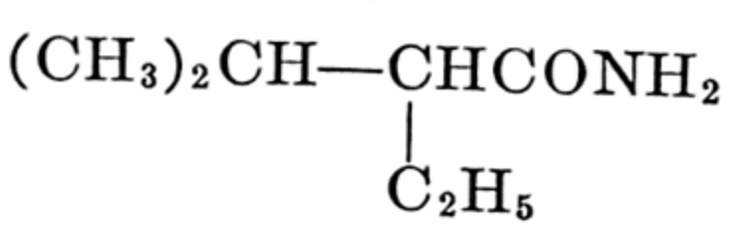
By replacing two or three of the hydrogen atoms of the methyl group of acetamide by alkyls, or by two alkyls and one chlorine or bromine atom, useful sedatives have been found, for example, Novonal (diethylallylacetamide, IX-34), Declonal (diethyl-α-chloroacetamide, IX-35), and Neodorm (ethylisopropylacetamide, IX-36).



(IX-34)



(IX-35)



(IX-36)

[16] Lehman and Knoefel, *J. Pharmacol. Exptl. Therap.*, **63,** 453 (1938).

As in the group of simple amides, branching or halogenation of the alkyl groups increases the sedative activity of *acyl ureas*. Carbromal (diethylbromoacetyl urea, IX-37), Bromural (Adalin, bromisovaleryl urea, IX-38), and Sedormide (allyl-isopropylacetyl urea, IX-39) are widely used sedatives. Some diacyl ureas exhibit hypnosis comparable to that of diethyl barbiturate, but even moderate duration of action in animals can be attained only by relatively large doses. Analgesia frequently accompanies the hypnotic effect.

The syntheses of the three acylureas mentioned in the preceding paragraph start from the corresponding alkyl or dialkylmalonic acids which are decarboxylated to alkyl or dialkylacetic acids. The chlorides of these acids react with urea to yield the acetyl ureas which, if necessary, can be halogenated in the α-position (examples a and b).

(a) $(C_2H_5)_2C(CO_2H)_2 \xrightarrow[2.\ SOCl_2]{1.\ -CO_2} (C_2H_5)_2CHCOCl \xrightarrow{Urea}$

$(C_2H_5)_2CHCONHCONH_2 \xrightarrow{Br_2} (C_2H_5)_2\overset{\displaystyle Br}{\overset{|}{C}}CONHCONH_2 \cdot HBr$

(IX-37)

(b) $(CH_3)_2CHCH(CO_2H)_2 \xrightarrow{3\ steps} (CH_3)_2CHCH_2CONHCONH_2$

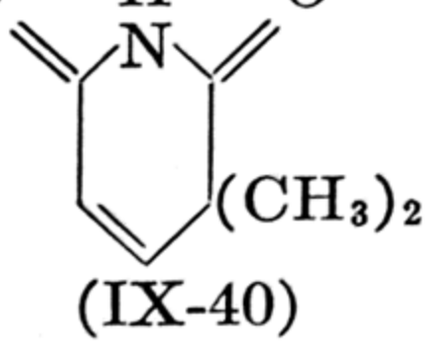
$\xrightarrow{Br_2} (CH_3)_2CHCHBrCONHCONH_2$

(IX-38)

(c) $(CH_3)_2CHC(CO_2H)_2$ (with $CH_2CH{=}CH_2$) $\xrightarrow{3\ steps} (CH_3)_2CHCHCONHCONH_2$ (with $CH_2CH{=}CH_2$)

(IX-39)

The most successful urea in the field of hypnotics is the cyclic derivative Persedon, 3,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyridine (IX-40). It may be that the structural analogy to dialkylbarbituric acids ex-



(IX-40)

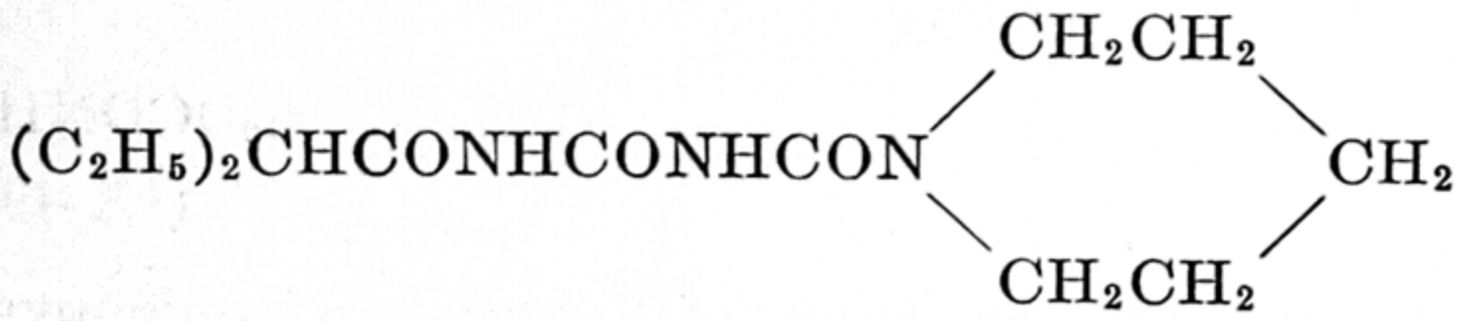
pressed in its formula contributes toward the intensification of the sedative properties of this drug.

The known low toxicity of derivatives of biuret ($H_2NCONHCONH_2$)

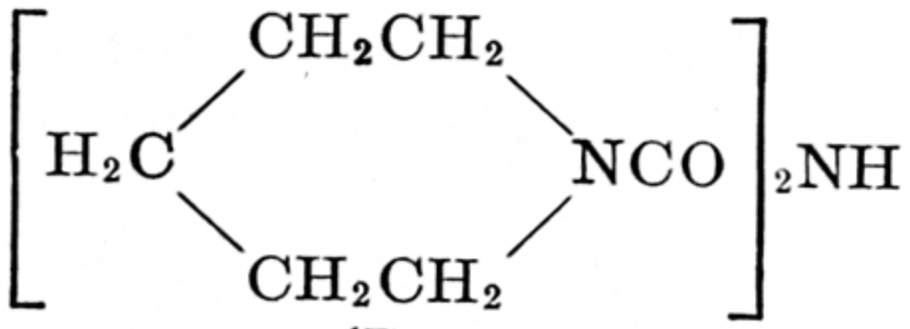
suggested to Hill and Degnan[17] the testing of acylbiurets as hypnotics. Using the Billeter reaction[18] they condensed dialkylacetyl isocyanates (IX-41) with alkylureas (IX-42) and obtained thereby the dialkylacetyl biurets (IX-43) in over 80% yield.

$$\underset{\text{(IX-41)}}{R_2CHCONCO} + \underset{\text{(IX-42)}}{R'NHCONH_2} \rightarrow \underset{\text{(IX-43)}}{R_2CHCONHCONHCONHR'}$$

These compounds compare favorably with barbital in hypnotic effect and lack all anesthetic action. As much as 500 mg./kg. has no permanent ill effect on test animals. The most active compound in this series is 1-diethylacetyl-5,5-pentamethylene biuret (IX-44). A particularly low toxicity is exhibited by 1,1,5,5-bis(pentamethylene) biuret (IX-45) which also has a very favorable hypnotic index.[19]



(IX-44)



(IX-45)

VII. URETHANS[20]

Ethyl urethan (ethyl carbamate, $H_2NCOOC_2H_5$) has been employed as an analgetic, anesthetic and clinical hypnotic at various periods. Although its high toxicity could not assure it but passing attention the chemical lead divulged by this compound, a combination of amide and ester groups, invited structural variations along the lines which had lead to more potent and less toxic derivatives of amides and ureides. Unfortunately, as potency increases in the series of branched or halogenated urethans, so does toxicity, and none of these compounds have gained a lasting foothold in therapeutic practice. Hedonal (1-methylbutyl urethan, IX-46), Vol-

[17] Hill and Degnan, *J. Am. Chem. Soc.*, **62,** 1595 (1940).
[18] Billeter, *Ber.*, **36,** 3213 (1903). Baeyer and Co., German Pat. 275,215.
[19] Anderson, Ch'eng, P'an, Sah, and Lu, *Science*, **95,** 254 (1942).
[20] Rice, *J. Am. Pharm. Assoc.*, **33,** 289 (1944); this article contains a general review of hypnotics.

untal (2,2,2-trichloroethyl urethan, IX-47), Aleudrin (α,α'-dichloroisopropyl urethan, IX-48) and Aponal (*tert*-amyl urethan, IX-49) may serve as examples of this series.

Voluntal (IX-47) is synthesized by condensation of trichloroethanol with phosgene in the presence of quinoline and subsequent treatment with ammonia according to the scheme:

$$Cl_3CCH_2OH + COCl_2 \rightarrow CCl_3CH_2OCOCl \rightarrow CCl_3CH_2OCONH_2$$
(IX-47)

Other urethans are prepared by analogous routes.

$CH_3(CH_2)_2CH(CH_3)OCONH_2$
(IX-46)

$(ClCH_2)_2CHOCONH_2$
(IX-48)

$(CH_3)_3CCH_2OCONH_2$
(IX-49)

A combination of molecular proportions of Voluntal and aminopyrine has a stronger hypnotic effect than the urethan could have by itself. This potentiation is similar to that achieved by mixing barbiturates with certain analgetics, and has sometimes been spoken of as Bürgi's principle of cumulative action.

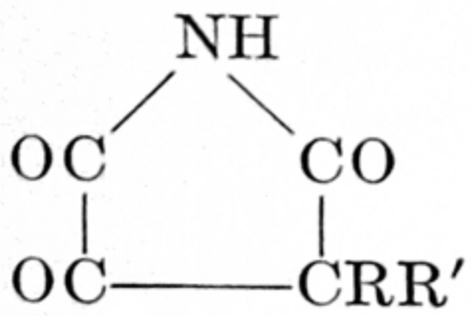
Aromatic urethans exhibit local anesthetic activity (Chapter VIII), a fact which affects testing for hypnotic activity in the urethan series. Many urethans are habit-forming and have diuretic properties, and this has slowed down interest in this field. It should be mentioned that urethan inhibits mitosis (Chapter XXVII), and that certain aromatic urethans (physostigmine, Prostigmin etc., Chapter XXI) are powerful inhibitors of cholinesterase. It is not known whether the hypnotic effects of urethans are based on a similar pharmacodynamic mechanism.

$$CH_3CH_2CH_2CH\text{—}C(C_2H_5)CONH_2$$
$$\quad\quad\quad

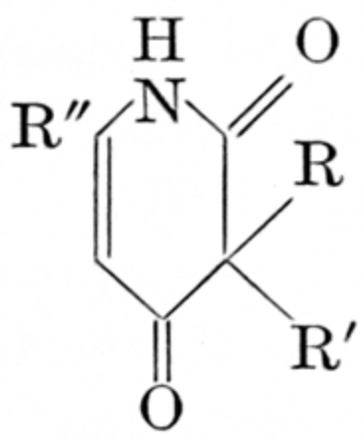
Hypnotics And Sedatives

VIII. HYDANTOINS, PYRIDONES, PYRROLIDONES, AND THIAZOLIDONES

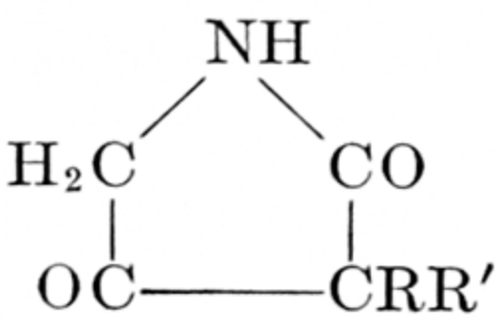
Compounds in these series are mentioned here only briefly because they share with the 5,5-dialkylbarbituric acids the structural segment RR′C—CONH— which seems to be the pharmacophoric feature of these types and is encountered also in the dialkylacetylureas, -biurets, etc. With the exception of Persedon (IX-40) no useful hypnotic has been encountered among these compounds. The importance of disubstituted hydantoins as anticonvulsants will be discussed in Chapter X. Type formulas of the series in which searches for hypnotics have been made are shown here.



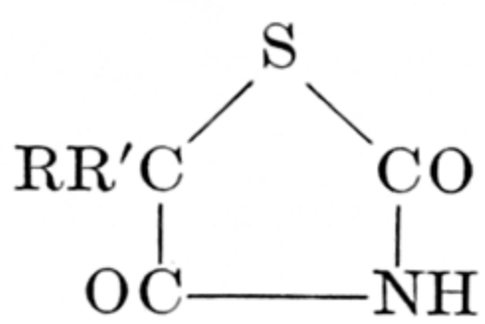
Hydantoins



Pyridones



Pyrrolidones



Thiazolidones

IX. ALIPHATIC DISULFONES AS HYPNOTICS

The postulate that a combination of certain chemical and physical properties is prerequisite for hypnotic action, and that the most important chemical property is a sufficient resistance to *in vivo* degradation and premature elimination, has stimulated the search for hypnotics in many different structural series. Although their activity was discovered accidentally by Baumann and Kast in 1888,[22] development of the aliphatic disulfones $R_2CH(SO_2R)_2$ could, in retrospect, be traced to this kind of reasoning. In the light of our present knowledge, these sulfones do not occupy a unique position. The bacteriostatic aromatic sulfones (Chapter XXXVI) depress functions of both the parasitic and the host cells, and an explanation of the mechanism of their action, based on metabolite antagonism, has been proposed (Chapter XXXII). It may be, therefore, that a similar mechanism could be evolved for the hypnosis caused by aliphatic sulfones. That they are not general cell depressants is shown by their lack of analgetic power. They are slowly absorbed, poorly soluble in water, but also slowly excreted giving rise to chronic toxicity symptoms manifested even initially by severe depression which persists after termination of administration. Before the introduction of the barbiturates and other less toxic hypnotics in the first decade of this century, three of

[22] Baumann and Kast, *Z. physiol. Chem.*, **14**, 52 (1888).

the disulfones (Sulfonal, Trional and Tetronal) were used often but they have been almost completely abandoned.

The narcotic activity of these compounds increases from Sulfonal (IX-52) through Trional (IX-53) to the higher homolog Tetronal (IX-54),

$(CH_3)_2C(SO_2CH_3)_2$ (IX-51)

$(CH_3)_2C(SO_2C_2H_5)_2$ (IX-52)

$C_2H_5C(CH_3)(SO_2C_2H_5)_2$ (IX-53)

$(C_2H_5)_2C(SO_2C_2H_5)_2$ (IX-54)

the lower tetramethyl homolog (IX-51) being inactive.

Similar increases are observed in many other series, e.g., the barbiturates, where the 5,5-dimethyl derivative also shows no activity. In the series of tertiary carbinols, the narcotic activity also rises from $(CH_3)_2(C_2H_5)COH$ through $(CH_3)(C_2H_5)_2COH$ to $(C_2H_5)_3COH$.

Sulfonal has been synthesized by two major routes. Acetone may be condensed with ethyl mercaptan, and the thioacetal from this reaction can be oxidized with permanganate to the disulfone:

$$(CH_3)_2CO + 2\ HSC_2H_5 \rightarrow (CH_3)_2C(SC_2H_5)_2 \rightarrow (CH_3)_2C(SO_2C_2H_5)_2$$
(IX-52)

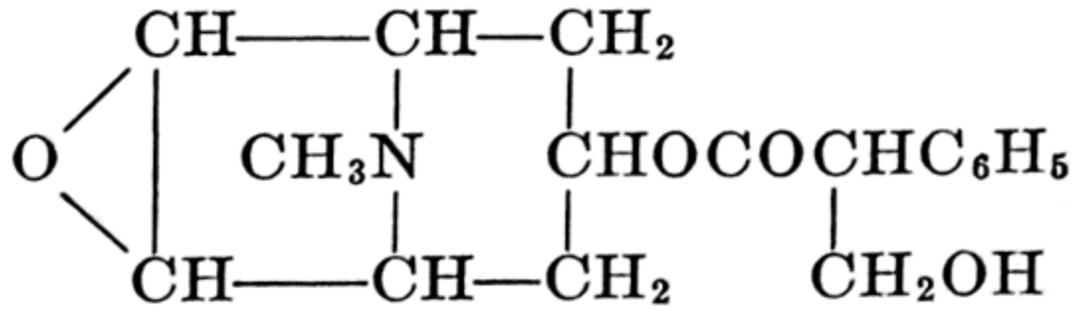
The second approach makes use of the activating effect of the sulfone groups on the enolizable hydrogen atom in ethylidene diethyl sulfone (IX-55) which can be carbon-alkylated with methyl iodide in alkaline solution.

$$CH_3CH(SO_2C_2H_5)_2 \xrightarrow{OH^-} CH_3C^-(SO_2C_2H_5)_2$$
(IX-55)

$$\xrightarrow{CH_3I} (CH_3)_2C(SO_2C_2H_5)_2$$
(IX-52)

X. SCOPOLAMINE

Scopolamine, also called hyoscine (IX-56), combines mydriatic and atropine-like properties with a peculiar depressant effect on the central



(IX-56)

nervous system which produces sleep in extremely small doses of about 0.007 mg./kg. Because of its low margin of safety it is not used as a hypnotic but has found wide application in obstetrical practice to induce twilight sleep. It has also been claimed to prevent motion sickness. Forensically, it has been chosen as an ingredient of truth sera since it depresses dishonest intellectual resistance to a point where the normal, socially responsible functions gain over abnormal psychological impulses. A similar effect can also be secured with small non-hypnotic doses of Pentothal (IX-22).

CHAPTER X

Anticonvulsant Drugs

I. CONVULSIONS AND EPILEPSY

Anticonvulsant drugs are compounds which prevent epileptic seizures and control convulsions produced by the seizures.

Epilepsy was regarded throughout the Middle Ages as a manifestation of the presence of an evil spirit in the afflicted individual. The best way of treatment suggested was to exorcise the evil spirit and thereby urge it to abandon the body during the convulsions. Proof of the presence of such a spirit was usually associated with the appearance of foam on the mouth of the epileptic patient, bleeding, unconsciousness, and various outcries during the attacks.

The introduction of electroencephalograms demonstrated that epileptic convulsions are characterized by an excessive discharge of electricity from neurons of the cerebral cortex. As with other electrical manifestations in any part of the organism, the cerebral neuronal discharges must be caused by chemical reactions. The nature of these chemical reactions is unknown. Normally the reactions of the brain cells produce electric waves with a small amplitude and a rapid rate. Any decrease or increase of cerebral chemical activity results in an irregular out-of-phase discharge. If a group of neighboring cells which ordinarily may have been slightly different from one another begins to discharge at an abnormally slow or fast rhythm a mechanism is set in motion which can lead to a convulsion.

Among the hypotheses concerning the nature of the reaction leading to abnormal electric discharges is the assumption that reactions of electrolytes which proceed across semipermeable brain cell membranes may become abnormal and will produce alterations in the normal potential of the brain waves. Abnormal reactions have also been sought in the unusually high or low carbon dioxide blood level in various types of seizures, in observed changes of the pH of the cortex during convulsions, and in the fact that petit mal attacks can be cut short by inhaling carbon dioxide. Overventilation, i.e., excessive use of oxygen by the brain cells, may precipitate attacks. In epileptic patients, grand mal seizures have been brought about by administration of the extract of the posterior pituitary lobe; on the other hand, the tendency for seizures is decreased by a ketogenic diet.

Chemicals which can produce convulsions have been shown to cause alterations affecting the respiration of tissue slices in the Warburg apparatus. Among these are the analeptic drugs, camphor, strychnine, and picrotoxin. By what mechanisms these drugs produce abnormal discharges of electric brain waves is unknown.[1] During the last decade, insulin and Metrazol have been used in mental patients requiring shock therapy, and the electrical discharges of the convulsions observed during this treatment resemble to some extent those of epileptic convulsions as shown by their electroencephalogram. The drugs to be discussed in this chapter are compounds which counteract epileptic seizures in man, and counteract seizures produced by insulin, Metrazol or electric stimulations of the cerebral cortex in animals or in man.

Not all types of epilepsy are characterized by convulsions, and consciousness is not always lost. Even though striking external symptoms may not be observable, violent alterations of the electrical discharges can be registered encephalographically in all cases. If consciousness is lost and a dreamy state ensues, but convulsions are not observed, the attacks are known as minor epilepsy or *petit mal*. With general convulsions and loss of consciousness the convulsant seizures are spoken of as major epilepsy or *grand mal*. Localized convulsions which may occur without the loss of consciousness are called *Jacksonian seizures* or cortical epilepsy; *psychomotor seizures* are characterized by certain encephalographic differences.

Grand mal is characterized by abnormally fast brain waves, petit mal by alternately slow and fast waves. Their sequence, caused by improper functioning of the mechanism which regulates the rhythm of the brain waves, has been called a paroxysmal cerebral dysrhythmia. Details of the causes of the dysrhythmias are not yet understood. They may be hereditary, or due to abnormalities of the brain or any other part of the body. Epilepsy appears often shortly before puberty, and no statistical differences between its incidence in males and females have been noted. Jacksonian seizures may occasionally be caused by a scar on the motor cortex of the brain but cerebral lesions are not the rule in epileptic patients. Suggestions that epilepsy may be caused by allergies, and influenced by antihistaminic drugs, have not received much attention.

Putnam and Merritt[2] have suggested that the abnormalities leading to convulsions may be due to the inability of the brain to utilize a metabolite in a normal manner and thereby to maintain normal reactions of these

[1] Toman and Goodman, *Physiol. Revs.*, **28,** 409 (1948). Toman and Davis, *J. Pharmacol. Exptl. Therap.*, **97,** 425 (1949).

[2] Putnam and Merritt, *Science*, **85,** 525 (1937). Merritt and Putnam, *Arch. Neurol. Psychiat.*, **39,** 1003 (1938); *Epilepsia*, **3,** 51 (1945).

materials. They pointed to the favorable effect of pyruvic acid and glucose on convulsions; the latter actually inhibits petit mal attacks. Vice-versa, these attacks may be precipitated by hypoglycemia. The question whether glucose, pyruvic acid, or perhaps lactic acid are convulsion-preventing metabolites is obscured by the effect of acetoacetic acid, a degradation product in fat metabolism, which acts in a similar manner as pyruvic acid. There are many types of convulsions in children not due to epilepsy. These seizures are not relieved by antiepileptic drugs since they may be due to gastrointestinal disturbances, infectious irritations, congestion of blood in the brain, diseases of the nervous system, rickets and many other conditions. The best treatment for such conditions consists in removing the causative irritation.

II. ASSAY OF ANTICONVULSANT DRUGS

An antiepileptic drug is assayed by techniques involving both electrical and chemical methods. Nevertheless, a drug which does not elevate the threshold of some convulsions may still be a good anticonvulsant. Dilantin, for instance, does not raise the threshold of seizures produced by Metrazol, but it is an excellent anticonvulsant used in grand mal and psychomotoric seizures. If it had been assayed only against Metrazol shock its usefulness would never have been discovered; its assay is based on its ability to raise the experimentally lowered threshold for the minimum seizures and to change the pattern of the convulsions caused by electroshock. This shows that more assays for anticonvulsants are needed. They should include modifications of the rhythm of the maximum seizures, a study of any elevation of the normal or experimentally lowered threshold for minimum electroshock convulsions, and protection against convulsions caused by Metrazol.

The change in the brain-wave pattern caused by maximum electroshock is the best laboratory screening test for a new drug. Usually only one electric shock needs to be given per animal. This procedure avoids alterations of the wave picture below the convulsive threshold. The maximum electroshock and the Metrazol tests together are considered necessary for a reliable preliminary screening. Promising drugs with low toxicity may then be screened in man, perhaps in volunteer psychiatric non-epileptic patients who are undergoing electroshock therapy in mental institutions.

In the laboratory, mice are prepared for the electroshock method by oral administration of the drug in solution or in tragacanth suspension. Electrodes are placed over the eyes of the animals after one hour and a direct current stimulus of one-tenth ampere for one-third second is applied. This is three times the current necessary to produce maximum seizures. If convulsions caused by Metrazol are to be observed in mice, the drug is

administered, and after one hour 100 mg./kg. of Metrazol in water solution is injected subcutaneously to start the test.

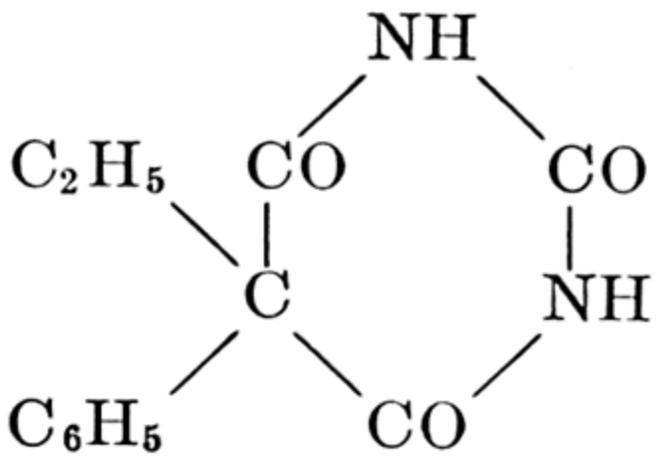
III. THE BARBITURATES

In doses sufficient to produce anesthesia practically all hypnotics relieve convulsive attacks. This is true especially in the group of barbiturates; phenylethylbarbituric acid (phenobarbital, Luminal, X-1) has proved to be one of the most effective anticonvulsants in non-hypnotic doses. Synthesized in 1911, it was introduced by Hauptman[3] as an anticonvulsant superior to inorganic bromides. Its advantages are particularly the rapid onset of its action, and its control of severe acute attacks of grand mal. In contrast to its usefulness in this form of epilepsy, it actually aggravates attacks of cortical epilepsy. The reason for this discrepancy may be the character of the electric waves emitted by the brain. They are abnormally fast in grand mal and alternately slow and fast in petit mal. Phenobarbital slows down brain waves and therefore has a therapeutic effect on these two conditions. In Jacksonian seizures the waves are unusually slow, and therefore the further slowing down by the drug aggravates this condition.

The anticonvulsant properties of phenobarbital may also be utilized in tetanus, cerebral hemorrhage and convulsions caused by drugs, especially if they occur during general anesthesia. In experimentally produced convulsions phenobarbital protects against Metrazol shock at low dosages; it also offers protection against electroshock but not without the side-effect of excitement followed by depression and ataxia.

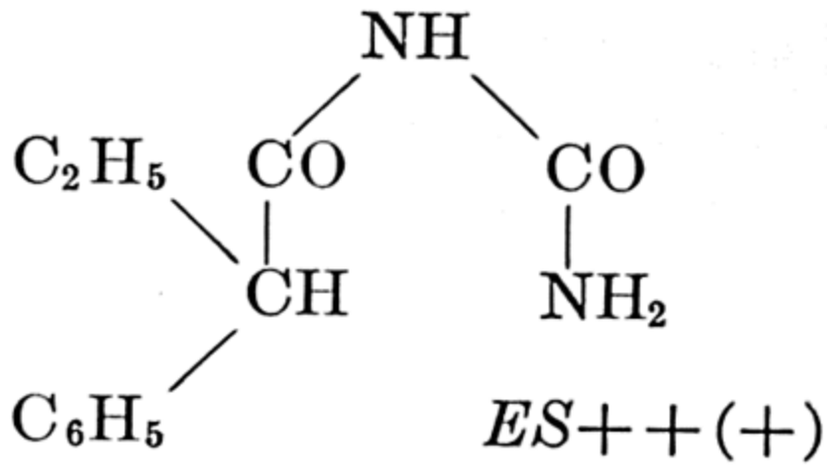
The chemical fate of phenobarbital and its biochemical role in interfering with a reaction which leads to convulsive symptoms is unknown. Although suggested as an explanation of its action,[2] it has never been proved that the trioxypyrimidine ring of the drug is opened and a degradation product, perhaps an amide or noncyclic ureide, is the actual carrier of anticonvulsant activity. Neither has it been proved that any simple aromatic compound, perhaps a derivative of benzoic acid, is formed by oxidative breakdown and interferes with some hypothetical abnormal convulsant metabolite. However, a purely chemical study of compounds containing non-cyclic fragments of the trioxypyrimidine system of phenobarbital has furnished a lead to successful drugs. Suitable dissections of the molecule of phenobarbital (X-1) could yield 2-phenyl-butyrylurea (X-2), N-methyl-2-phenylbutyramide (X-3), or 2-phenylbutyramide (X-4). The ureide (X-2) does not counteract Metrazol induced convulsions but it protects the animal completely against electroshock for which phenobarbital is only of limited value.

[3] Hauptmann, *Münch. med. Wochschr.*, **59,** 1907 (1912).



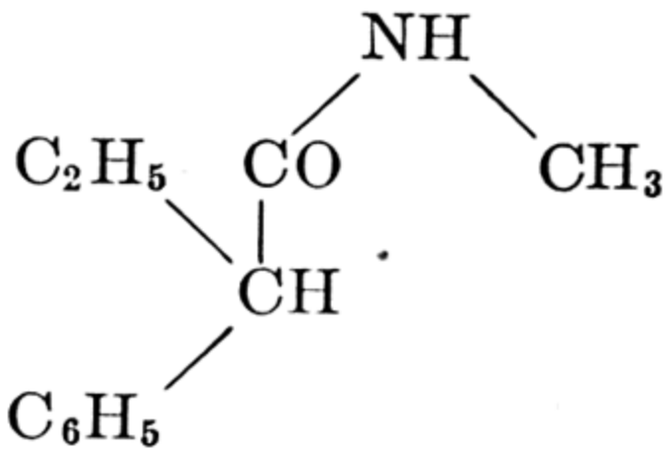
(X-1)

ES++
M ++



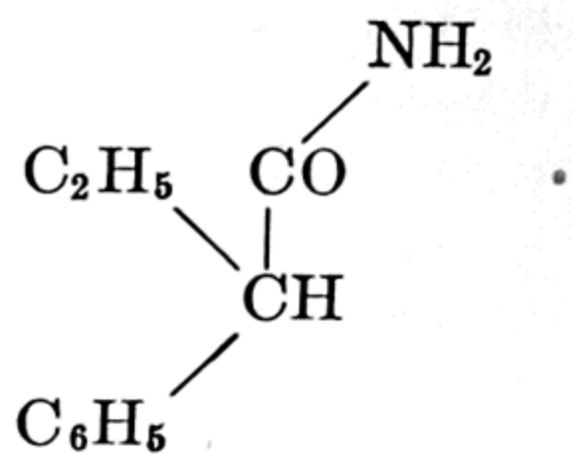
(X-2)

ES++(+)
M 0



(X-3)

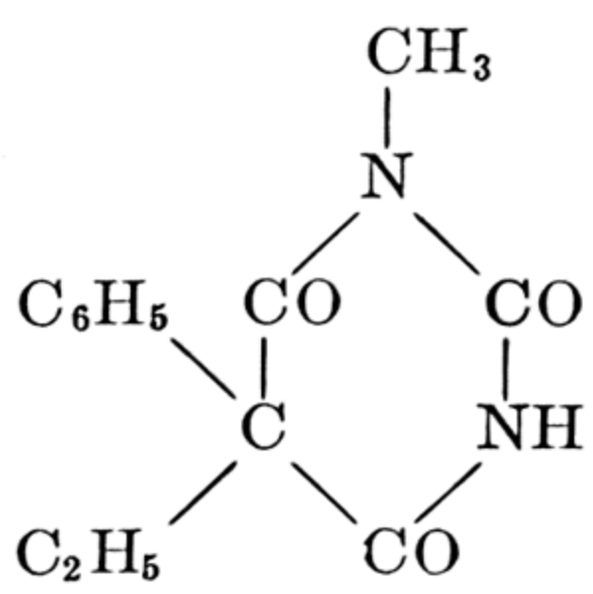
ES(+)
M 0



(X-4)

ES++
M 0

The discovery of the activity of this ureide has led to the pharmacological study of many analogous derivatives some of which are shown in Table I. While phenobarbital and its l-methyl derivative Prominal (Mebaral, X-5) are among the most widely used drugs in grand mal seizures,



(X-5)

phenylacetylurea (Phenurone, $C_6H_5CH_2CONHCONH_2$) is now often employed in the treatment of petit mal as an outcome of these studies.[4] They have also disclosed that the absence of activity against Metrazol shock observed in compounds (X-2,3,4) and many of their analogs does not necessarily exclude usefulness in petit mal; in the same sense, inactivity against electroshock must not be taken as an indication that trials against grand mal seizures will be fruitless.

[4] Spielman, Geiszler and Close, *J. Am. Chem. Soc.*, **70,** 4189 (1948). Davidson and Lennox, *Dis. Nerv. System*, **11,** 167 (1950).

[5] Some of the data were announced by Spielman, and by Long, *Abstracts*, First National Medicinal Symposium, American Chemical Society, Ann Arbor, 1948.

TABLE I. ANTICONVULSANT ACTIVITY OF EXPERIMENTAL DRUGS[5]

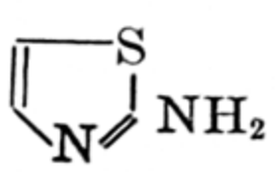
Compound	Formula	*ES*	*M*
	(a) *Ketones and Ketone Derivatives*		
Acetophenone	$C_6H_5COCH_3$	+(+)	
Acetophenone oxime	$C_6H_5C{=}NOH(CH_3)$ (probably hydrolyzed to ketone)	+(+)	
Propiophenone	$C_6H_5COC_2H_5$	+(+)	
Butyrophenone	$C_6H_5CO(CH_2)_2CH_3$	+(+)	
Valerophenone	$C_6H_5CO(CH_2)_3CH_3$	+(+)	
Isovalerophenone	$C_6H_5COCH_2CH(CH_3)_2$ (most active ketone)	++(+)	
Benzylmethyl ketone	$C_6H_5CH_2COCH_3$	++	
Benzylmethyl ketoxime	$C_6H_5CH_2C(CH_3){=}NOH$	+(+)	
Dibenzyl ketone	$(C_6H_5CH_2)_2CO$	+(+)	
Benzophenone	$(C_6H_5)_2CO$	+	
Diethyl ketone	$(C_2H_5)_2CO$ (large doses)	+(+)	
Paraldehyde	$(CH_3CHO)_3$ (large doses)	+(+)	
	(b) *Sulfides, Sulfoxides, Sulfones*		
Ethyl phenyl sulfide	$C_6H_5SC_2H_5$	+(+)	
Ethyl phenyl sulfoxide	$C_6H_5SOC_2H_5$	+(+)	
Ethyl phenyl sulfone	$C_6H_5SO_2C_2H_5$ (tested clinically; convulsions recur)	++(+)	
Propyl phenyl sulfoxide	$C_6H_5SOC_3H_7$	+(+)	
Propyl phenyl sulfone	$C_6H_5SO_2C_3H_7$	+(+)	
Isopropyl phenyl sulfone	$C_6H_5SO_2CH(CH_3)_2$	+(+)	
Bis-(4-aminophenyl) sulfone	$(H_2NC_6H_4)_2SO_2$	+(+)	
4-Aminophenyl-2-amino-5-thiazolyl sulfone	$H_2NC_6H_4SO_2$ 	++	
	(c) *Ureides*		
Phenacetylurea (Phenurone)	$C_6H_5CH_2CONHCONH_2$ (effective in all 3 types of seizures	++(+)	+(+)
2-Phenylpropionylurea	$C_6H_5CH(CH_3)_3CONHCONH_2$	++(+)	
2-Phenylbutyrylurea	$C_6H_5CH(C_2H_5)CONHCONH_2$ (least toxic, most active in grand mal)	++(+)	
2-Phenyl-4-pentenoylurea	$C_6H_5CH(CH_2CH{=}CH_2)CONHCONH_2$	+(+)	++(+)
Isovalerylurea	$(CH_3)_2CHCH_2CONHCONH_2$	+(+)	+(+)
Trimethylacetylurea	$(CH_3)_3CCONHCONH_2$	+(+)	+(+)
2-Ethylbutyrylurea	$(C_2H_5)_2CHCONHCONH_2$	+(+)	+(+)
2,2-Dimethylbutyrylurea	$(CH_3)_2(C_2H_5)CCONHCONH_2$	+(+)	+(+)
2-Ethyl-3-methylbutyrylurea	$CH_3CH(CH_3)CH(C_2H_5)CONHCONH_2$	+(+)	++(+)
	(d) *Carbamates and Allophanates*		
Isopropyl Carbamate	$(CH_3)_2CHOCONH_2$	+(+)	+(+)
tert-Butylcarbamate	$(CH_3)_3COCONH_2$	+(+)	+(+)
Phenylurethane	$C_6H_5OCONH_2$	(+)	
(1,1-Dimethyl-)propyl allophanate	$(CH_3)_2C(C_2H_5)OCONHCONH_2$	+(+)	+(+)
(1-Methyl-1-ethyl)-propyl allophanate	$(C_2H_5)_2C(CH_3)OCONHCONH_2$	+(+)	+(+)
1-Phenylpropyl allophanate	$C_2H_5CH(C_6H_5)OCONHCONH_2$	+(+)	+(+)
	Miscellaneous Compounds		
Phenylsemicarbazide	$C_6H_5NHCONHNH_2$	(+)	
Phenylpropionamide	$C_6H_5CH_2CH_2CONH_2$	(+)	
Phenylglycol	$C_6H_5CHOHCH_2OH$	(+)	
Diphenylacetic acid	$(C_6H_5)_2CHCOOH$	(+)	

Table I lists a selection of drugs which have been found to inhibit convulsions in laboratory animals. *ES* signifies electroshock, *M* Metrazol shock. For tests using the electroshock method, one + signifies that the drug prevents convulsions when the animal is stimulated with no more than 2.5 to 3 times the electrical current necessary to transgress the normal convulsive threshold. Two plus signs mean a stimulation with a minimum of 50 milliamperes.

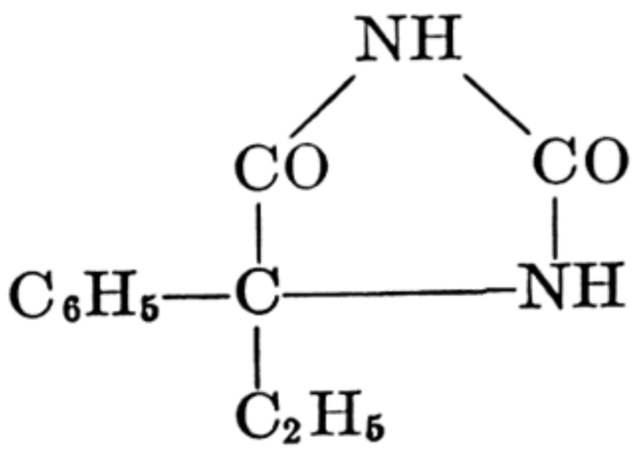
Complete protection from shock without toxic symptoms from the drug is expressed by ++(+), protection with some toxic symptoms by the symbol +(+). Partial protection is designated by (+).

The scanty correlation of structure and activity which can be observed among these compounds has not provided adequate guidance for further syntheses.

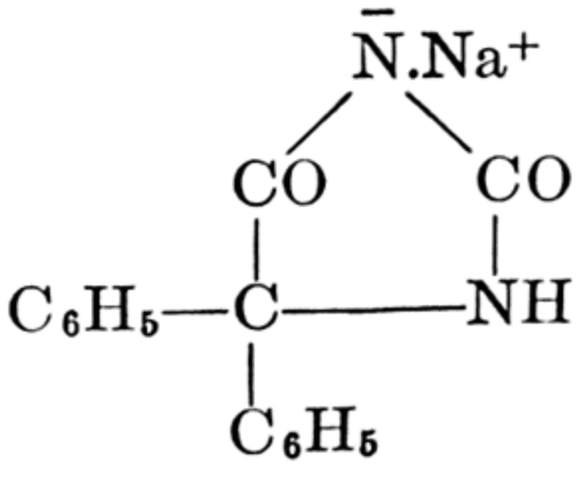
IV. THE HYDANTOINS

1. Derivatives and Their Functions

Related to the barbiturates are the 5,5-disubstituted hydantoins which may be regarded as glycolylureides. One of the earliest hydantoins to be tried as a sedative and anticonvulsant was the analog of phenobarbital, phenylethylhydantoin (X-6, nirvanol).[6] It was found to be active in various types of convulsions, particularly in chorea or Saint Vitus's dance in children who exhibit symptoms of irregular spasmotic involuntary movements of the limbs and facial muscles. However, the drug is no longer considered safe for the treatment of this disorder because of its toxicity.



(X-6)

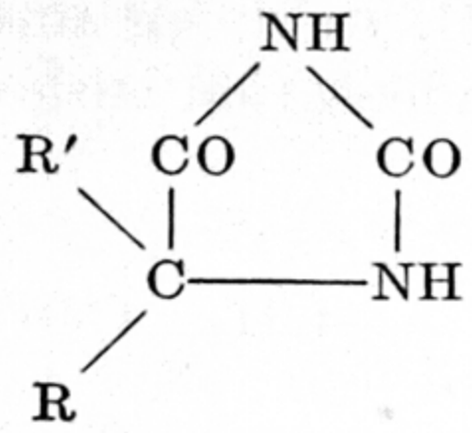


(X-7)

In 1938, Merritt and Putnam[2] found in a systematic study of hydantoins that the sodium salt of diphenyl hydantoin (Dilantin, X-7) had the greatest anticonvulsant activity combined with the lowest depressant effect of the many drugs they investigated. Their experiments were carried out on cats, and the drugs were tested against electroshock. Dilantin has been widely used in the control of grand mal and psychomotoric seizures since the discovery of its action. It seems to be selective in depressing

[6] Heyden, German Pats. 309,508; 310,426; 310,427; 335,994 (1914).

TABLE II. ANTICONVULSANT PROPERTIES OF 5,5′-DISUBSTITUTED HYDANTOINS[5]

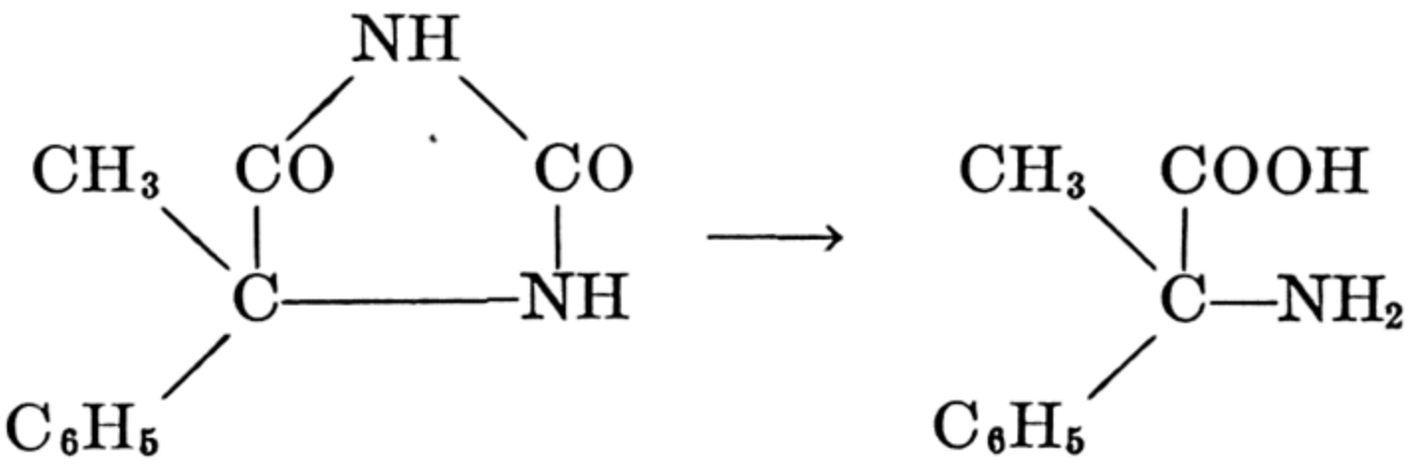


R	R′	*ES*
C_6H_5	$-CH_3$	+(+)
C_6H_5	$-C_2H_5$ (Nirvanol)	+(+)
C_6H_5	$-(CH_2)_2CH_3$	+(+)
C_6H_5	$-CH(CH_3)_2$	+(+)
C_6H_5	$-CH_2CH(CH_3)_2$	+(+)
C_6H_5	—cyclobutyl	+(+)
C_6H_5	$C_6H_5CH_2-$	+(+)
C_6H_5	$-CH_2OCH_3$	+
C_6H_5	$-CH_2OC_2H_5$	+(+)
C_6H_5	$-CH_2OCH(CH_3)_2$	+(+)
C_6H_5	$-CH_2OC_4H_9$	+(+)
C_6H_5	$-CH_2OC(CH_3)_3$	+(+)
C_6H_5	$-CH_2SCH_3$	0
C_6H_5	$-CH_2SCH_2CH(CH_3)_2$	+(+)
C_6H_5	$-CH_2SO_2CH_2CH(CH_3)_2$	+(+)
α-$C_{10}H_7$	$-CH_3$	+(+)
α-$C_{10}H_7$	$-C_2H_5$	+(+)
α-$C_{10}H_7$	$-CH_2CH_2CH_3$	+(+)
α-$C_{10}H_7$	$-(CH_2)_3CH_3$	+(+)
C_6H_5	$-C_6H_5$ (Dilantin)	+(+)
C_6H_5	2-Pyridyl-	++(+)
C_6H_5	3-Pyridyl-	++
C_6H_5	8-Quinolyl-	++
C_6H_5	2-Thienyl- (Thyphentoin)	+(+)
2-Thienyl	2-Thienyl-	++(+)
C_6H_5	$R'=C_2H_5, N^1$-CH_3 (Mesantoin)	++(+)

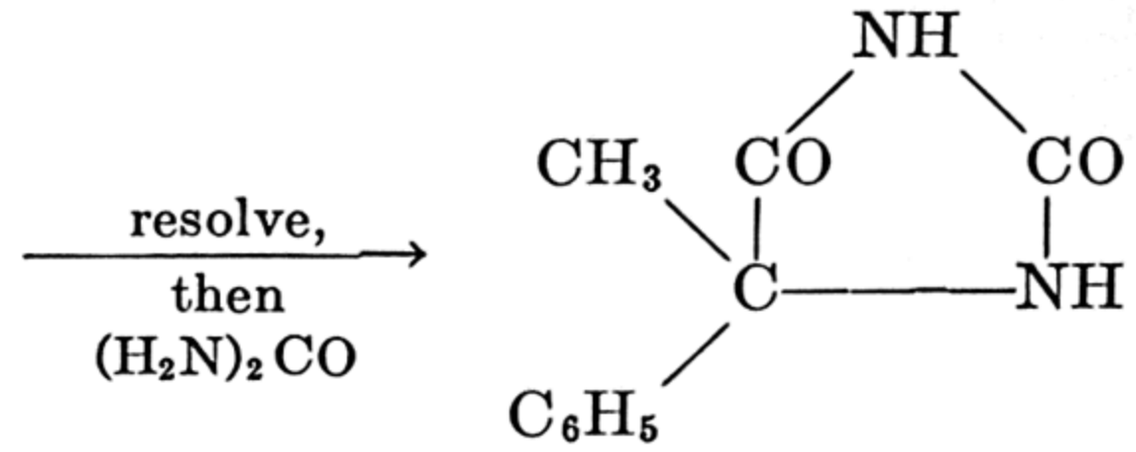
the motor cortex without producing sleep in therapeutic doses. The threshold of cortical excitability is raised 100 to 300% without hypnotic and toxic side-effects while a similar rise produced by phenobarbital is always accompanied by sleep. Whereas Dilantin does not necessarily improve the encephalogram of epileptic patients suffering from petit mal, it prevents such seizures in these individuals.

The lower homolog of nirvanol, 5-methyl-5-phenylhydantoin (X-8) very frequently causes a skin rash as its most characteristic toxic side-effect. This symptom is not exhibited by its dextrorotatory form, which points to the importance of sterical configuration in this series. The optical resolu-

tion of the racemic mixture can be carried out by hydrolyzing the hydantoin ring to α-phenylalanine (X-9), resolving this amino acid, and re-closing the hydantoin nucleus by condensation with urea.



(X-8) (X-9)

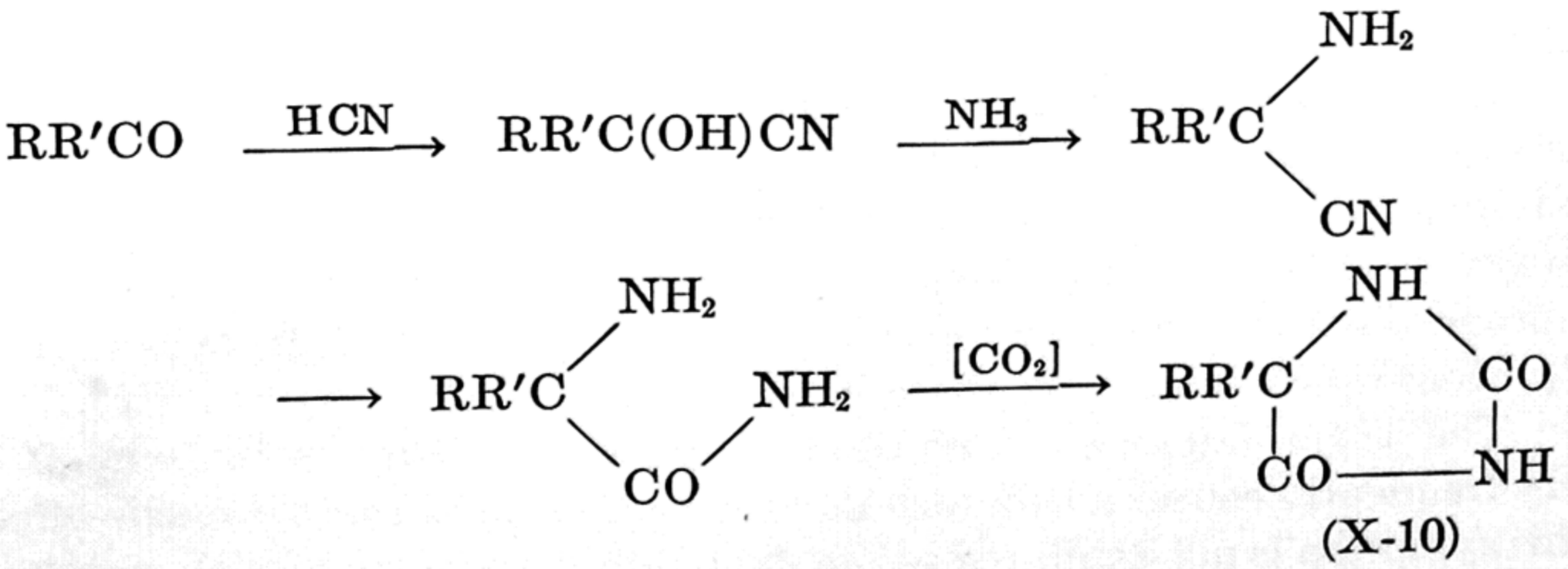


d-(X-8)

Some of the hydantoins tested in systematic studies of these compounds are listed in Table II. Activities are expressed by the same symbols used in Table I. Many other derivatives in which oxygen heterocycles are attached to position 5, or spirane type groups occupy both valences at this position, have been found inactive.

2. Synthetic Methods

The synthesis of 5,5′-disubstituted hydantoin derivatives (X-10) is carried out most conveniently by the method of Bucherer.[7] The ketone or its bisulfite addition product is heated with an alcohol solution of potassium cyanide and ammonium carbonate, the latter furnishing the ammonia and carbon dioxide required by the reaction:



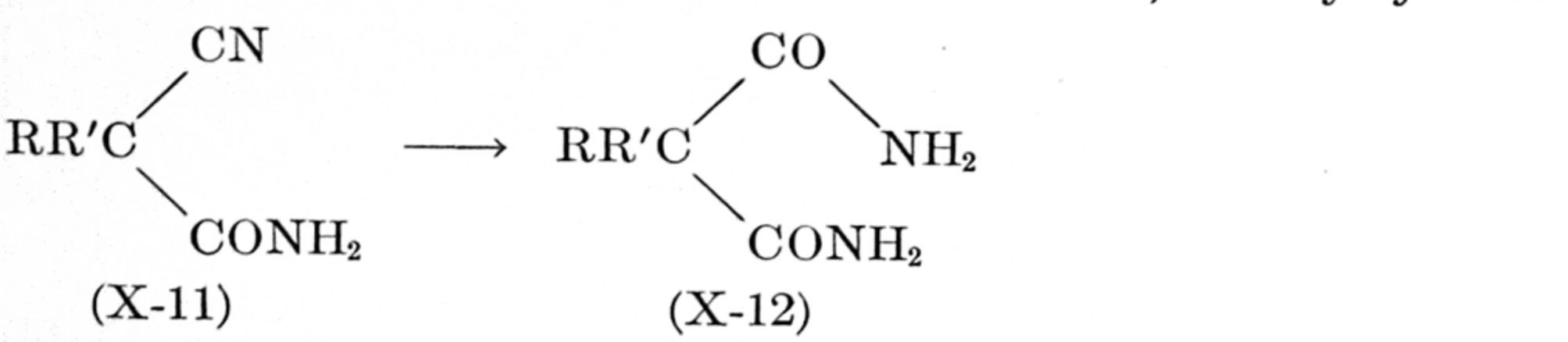
(X-10)

[7] Bucherer and Steiner, *J. prakt. Chem.*, **140,** 291 (1934). Compare Bergs, Germ. Pat. 566,094; Henze and Long, *J. Am. Chem. Soc.*, **63,** 1936 (1941).

As expressed by this scheme, the cyanohydrins are essential intermediates in this synthesis. It has been found that ketones incapable of cyanohydrin formation also do not furnish hydantoins by this reaction.

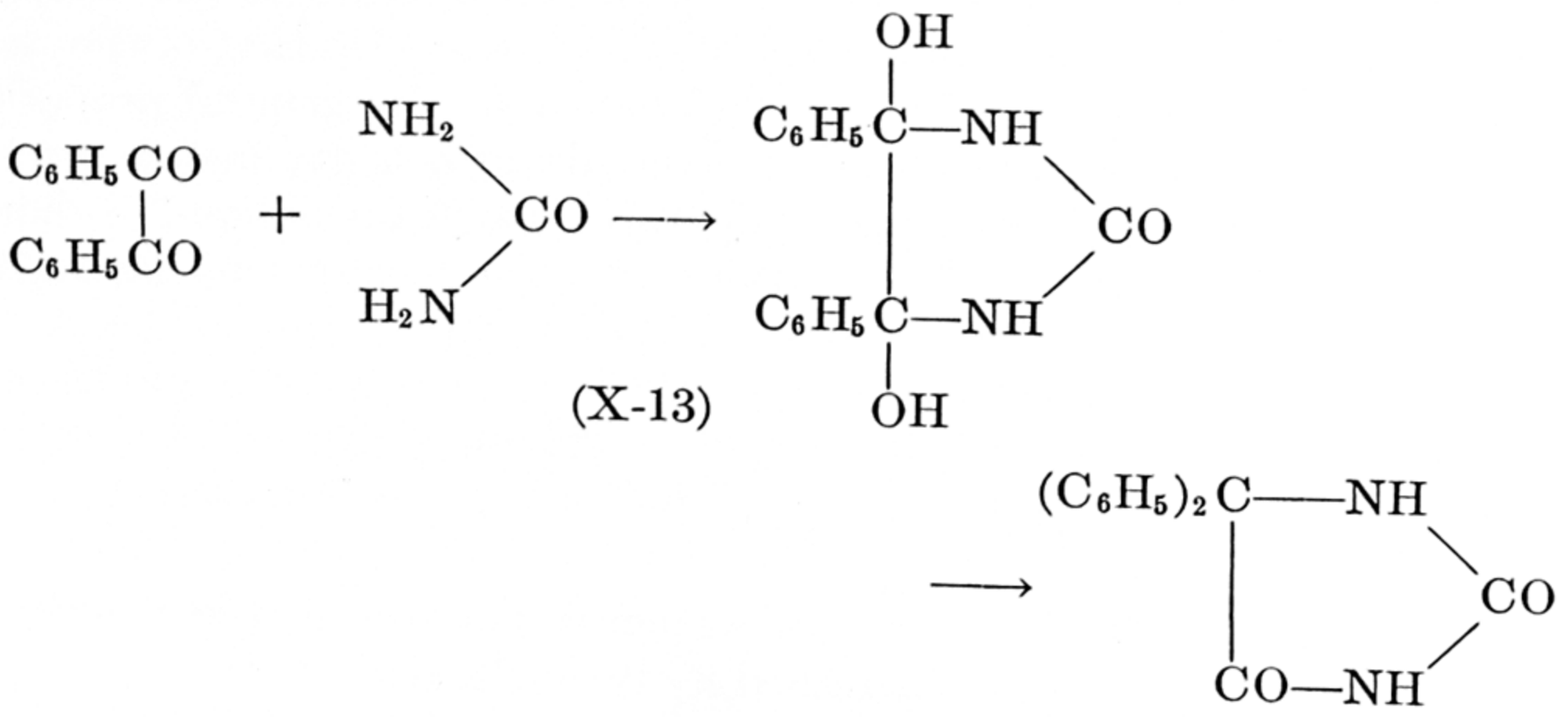
Modifications of the Bucherer approach make use of ethyl chlorocarbonate, phosgene or oxalyl chloride as sources of the elements of CO_2 for the final ring closure.

Under the influence of alkaline solutions of hypobromites, dialkylcyanoacetamides (X-11) are transformed via the corresponding malonamides (X-12), to isocyanates which isomerize to 5,5-dialkylhydantoins.



(X-11) (X-12) (X-10)

5,5′-Diarylhydantoins can be prepared also by condensing benzil with urea, and rearranging the intermediate pinacol (X-13). Hydantoins

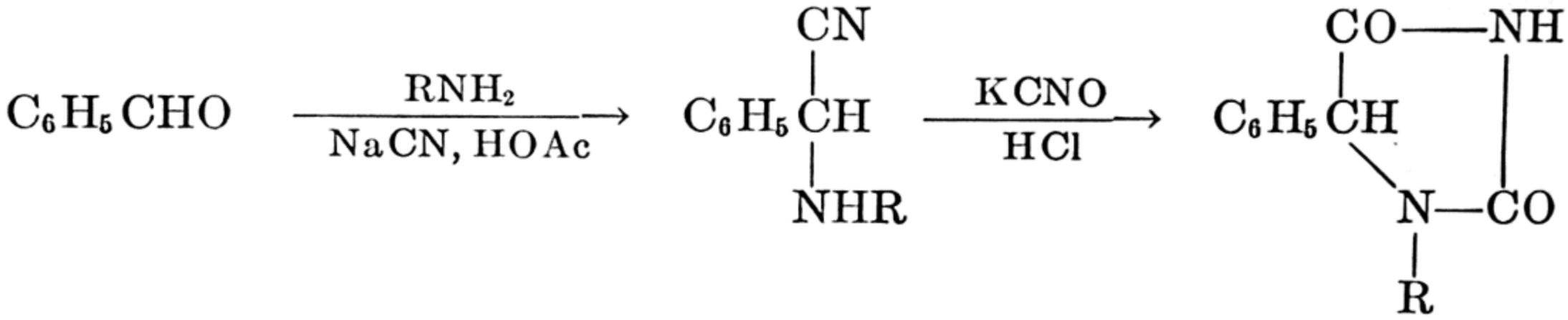


(X-13)

mono- or unsubstituted in position 5 are obtainable by a variety of reactions. These syntheses, their mechanism and their scope have been reviewed recently.[8]

[8] Tiffenau, Tchoubar, and Saislambert, *Bull. soc. chim. France*, **1947,** 445. Ware, *Chem. Revs.*, **46,** 403 (1950).

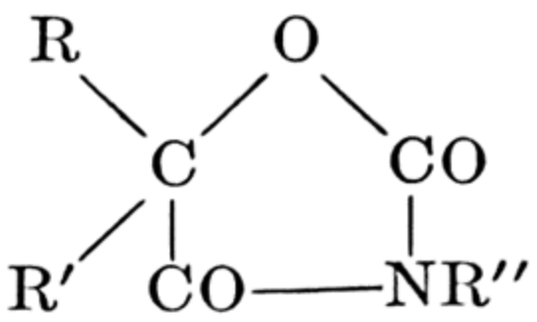
A high degree of inhibition of variously induced convulsions is attained in 1-alkyl substituted 5-phenylhydantoins (X-14) in which the alkyl group contains two to four carbon atoms.[9] Such compounds are prepared advantageously by converting benzaldehyde to the corresponding amino nitrile (X-15) which is then cyclized to the hydantoin with cyanic, and concentrated hydrochloric acid. Direct alkylation of 5-phenylhydantoins cannot be employed because the first alkyl group enters the ring at the 3-position. The propyl and allyl derivatives have received special attention.



(X-15) (X-14)

V. OXAZOLIDINEDIONES

As mentioned in the discussion of hypnotics, ring systems related to barbituric acid in general character and molecular shape are often suitable as parent stems of compounds with similar hypnotic activity. In the series of anticonvulsants, an analogous relationship holds between 5,5-disubstituted hydantoins and derivatives of comparable five-membered heterocyclic systems. The size and character of the substituents in the clinically most valuable derivatives is considerably at variance with that of the most useful hydantoins, and seems to be conditioned by the general properties of the ring. The most pronounced anticonvulsant activity in this type of compounds has been found among 3,5,5-trialkyloxazolidine-2,4-diones (X-16) which were first tested as hypnotics.[10] The most promising deriva-

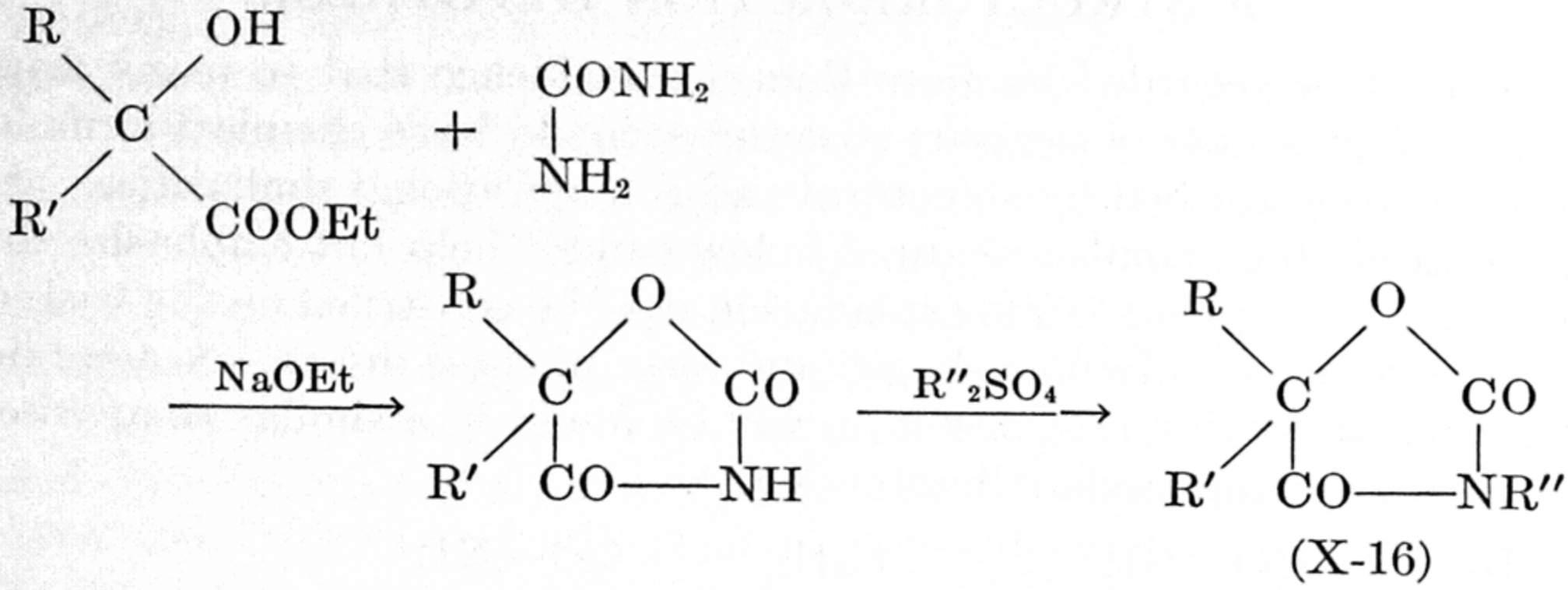


(X-16)

tive (Tridione, X-17) also possesses analgetic potency in the aspirin or aminopyrine range and is distinguished by its low toxicity.[11, 12]

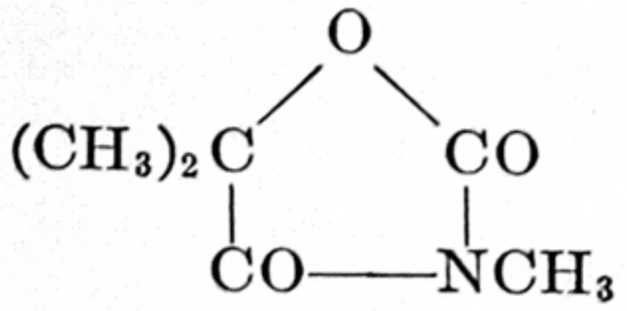
[9] Long, Miller, and Troutman, *J. Am. Chem. Soc.*, **70,** 900 (1948).
[10] Erlenmeyer, *Helv. Chim. Acta*, **21,** 1013 (1938).
[11] Spielman, *J. Am. Chem. Soc.*, **66,** 1244 (1944).
[12] Everett and Richards, *J. Pharmacol. Exptl. Therap.*, **81,** 402 (1944). Lennox, *J. Am. Med. Assoc.*, **129,** 1069 (1945). Perlstein and Andelman, *J. Pediat.*, **29,** 20 (1946).

The synthesis of these compounds has been studied by Stoughton[13] and by Spielman.[11] One of the methods involves the condensation of esters of glycolic acids with urea, followed by N-alkylation with alkyl sulfates.

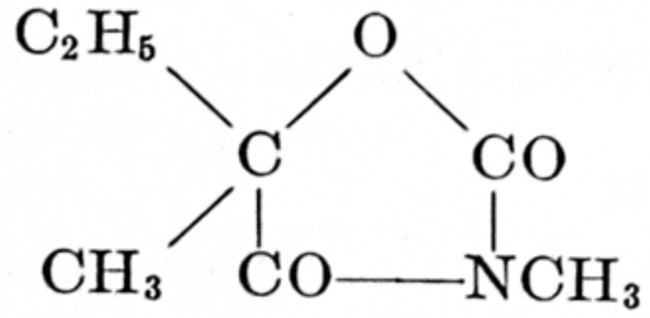


(X-16)

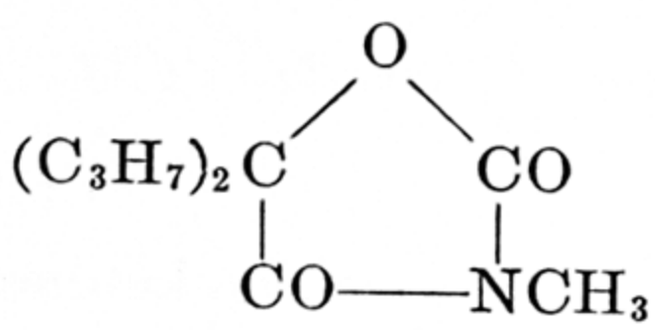
The most active of these compounds are the 3,5,5-trimethyl derivative (Tridione, X-17), the 3,5-dimethyl-5-ethyl derivative (Paradione, X-18), and 3-methyl-5,5-dipropyl-2,4-oxazolidinedione (Propazone, X-19). The first two compounds are both highly effective against Metrazol shock, and have slight activity against electroshock. They have been introduced as valuable drugs for the clinical treatment of petit mal. Tridione resembles the barbiturates and bromides in producing sedation at anticonvulsant dosages. Propazone has been found to inhibit only Metrazol type convulsions.



(X-17)

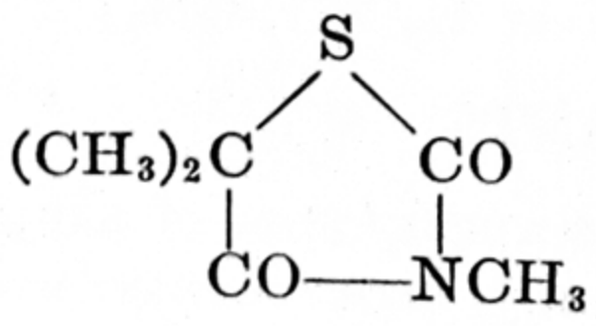


(X-18)

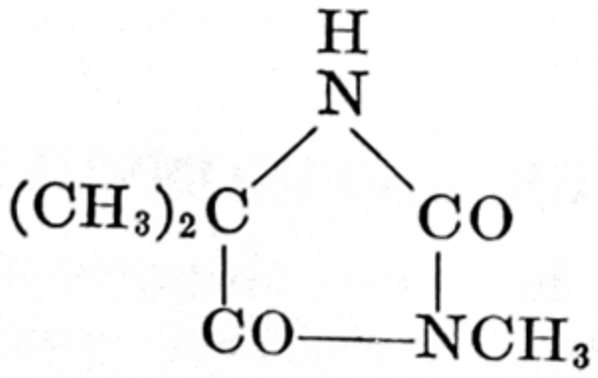


(X-19)

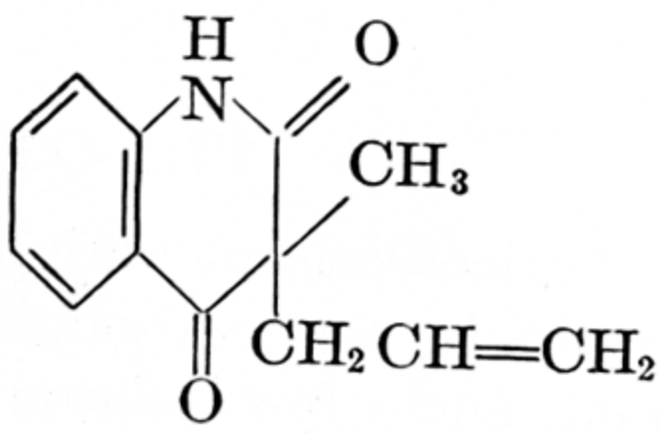
5,5-Diphenyl- and 5,5-dipropyloxazolidinedione-2,4 have shown good activity against experimental electroshock in rats. Replacement of the heterocyclic oxygen atom by sulfur (X-20) or nitrogen (X-21) leads to inactive compounds. A disubstituted quinolone, 2,4-dioxo-3-methyl-3-



(X-20)



(X-21)



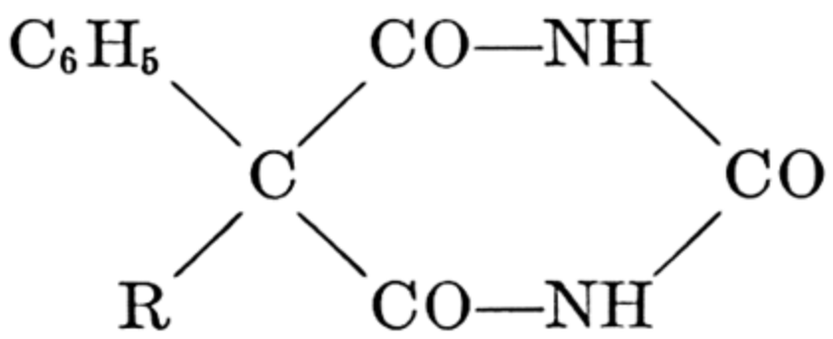
(X-22)

[13] Stoughton, *J. Am. Chem. Soc.*, **63,** 2376 (1941).

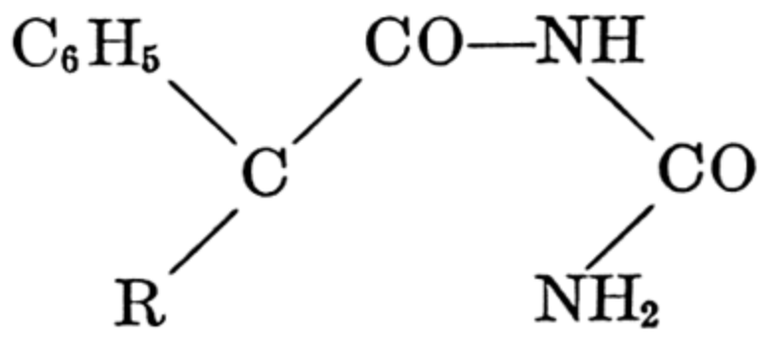
allyl-1,2,3,4-tetrahydroquinoline (X-22), has been recommended as an effective antispasmodic in epilepsy.[14]

VI. A STRUCTURE-ACTION HYPOTHESIS

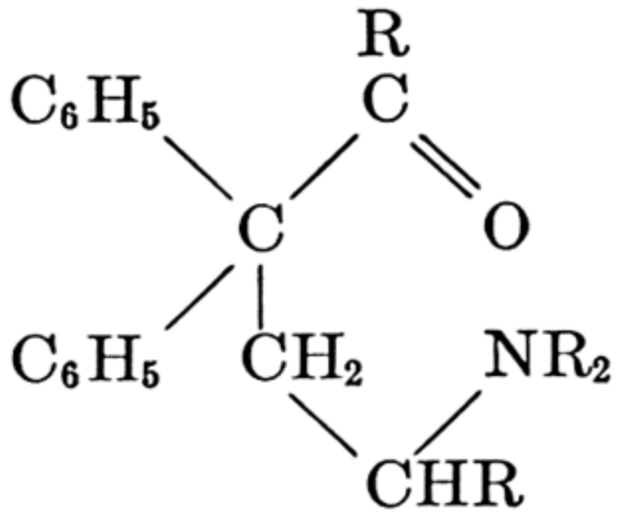
It must be regarded as more than a coincidence that so many drugs acting as depressants of nervous structures should have chemical formulas which are distinguished by structural and configurational similarities. An inspection of the formulas pictured below cannot help but emphasize this thought. A somewhat crude explanation may be construed on the basis of the similarities of molecular shapes and sizes of these drugs. A more detailed account of this interpretation will be found in a similar comparison of cholinergic compounds (Chapter XXI).



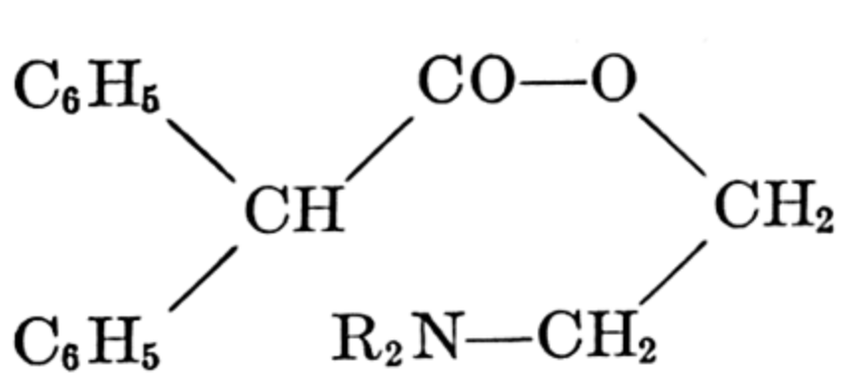
Barbiturates (hypnotics, anticonvulsants)



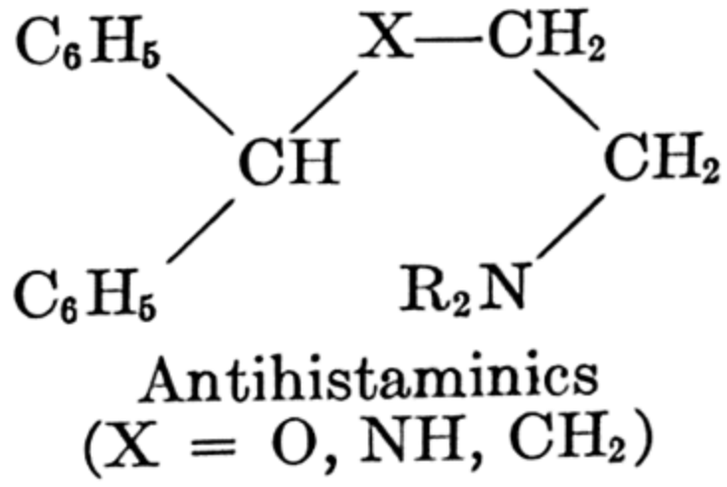
Ureides (anticonvulsants)



Amino ketones (e.g., Methadon, analgetics)



Antispasmodics



Antihistaminics
(X = O, NH, CH_2)

VII. OTHER ANTICONVULSANTS

Anticonvulsant activity has been observed in several types of simple compounds, and although they have been used only experimentally in animals and a few isolated clinical trials, they may provide useful leads for further work.

[14] Hoffmann-La Roche and Co., Swiss Pat. 216,826 (1941); *Chem. Abstr.*, **42,** 6382g (1948).

Alcohols and glycols have been found to possess anticonvulsant properties. Isopropyl alcohol has been claimed to be the most favorable anticonvulsant in animals,[15] and 2,2-diethyl-1,3-propanediol has proved equal to phenobarbital in Metrazol shock.[16] Analeptic phenethylamines such as Benzedrine and Dexedrine are fairly effective in petit mal.[17]

The bromide ion possesses certain antiepileptic properties. Bromine in organic linkage as found in many simple organic bromo compounds is physiologically inert. The pharmacological action of bromides is one of central depression which leads from slight sedation to deeper depression and finally to coma as the doses are increased.

Most tissues except nervous tissue cannot distinguish between bromide and chloride ions and are consequently not influenced by bromides. It has been suggested that bromides can displace chlorides but depletion of chlorides in nervous tissue does not cause central depression; bromides thus must have an effect of their own.

Whereas bromides can cancel out the convulsant effects of chemical or of electrical stimulation of the motor cortex, they are not depressant to this organ in contrast to other anticonvulsants, especially Dilantin. They elevate the convulsant threshold in electrically stimulated brains only about 50% in doses which cause definite hypnosis. Their action is slow in starting but, on the other hand, lasts unusually long in grand mal. For petit mal and chemically produced convulsions, bromides are useless.[2]

In connection with antiepileptic drugs, studies with malononitrile, $NCCH_2CN$, should be mentioned. This compound has shown promise in the treatment of psychiatric disorders.[18]

[15] Chu, Driver, and Hanzlik, *J. Pharmacol. Exptl. Therap.*, **92,** 291 (1948).
[16] Berger, *Proc. Soc. Exptl. Biol. Med.*, **71,** 270 (1949).
[17] Livingston, Kajdi, and Bridge, *J. Pediat.*, **32,** 490 (1948).
[18] Hartelius, *Am. J. Psychiatry*, **107,** 95 (1950).

CHAPTER XI

Analgetics

I. PAIN AND RELIEF FROM PAIN

Relief from pain by the use of drugs has been one of the oldest and most widely studied problems of medical art and science. Pain is the first manifestation of injury to tissues and the onset or the result of disease. It therefore is one of the most feared physiological reactions in animals and in man. Pain was considered as a feeling state until the end of the 19th century when it was realized that certain structures of the brain and the nervous system can give rise to the specific sensation of pain only. Nevertheless, the intimate connection with psychological reaction patterns makes it impossible to separate these factors in an analysis of pain experience.

In man, the most common manifestations of pain are headache, visceral pains, cardiac pain, neuralgia, pressure pains, root pains, pains caused by chronic arthritis and by dysmenorrhea or labor, muscle pains, toxic and traumatic pains. An excellent discussion of the nature of pain, its physiology, origin, conductance and reception has been published by Wolff and Hardy.[1]

Analgesia is the state of raising the threshold of pain. It may be brought about by drugs which, by tradition, are called analgesics. The grammatically more accurate term *analgetic* will be used in this Volume.

The pain threshold may be defined as the lowest perceptible intensity of pain, and is induced by a stimulus. The latter may serve as a measure of the variations of the pain threshold. If more stimulus is required the threshold of pain is said to be raised. If less stimulus is needed the pain threshold is said to be lowered.

Pain can be evoked by many different methods such as mechanical, chemical, thermal and electrical stimuli, and the only reliable measurements of variations in the threshold of pain consist in the verbal report of an individual exposed to a pain stimulus and instructed to describe his reaction. Since it is impossible to apply this method to laboratory animals no method of measuring a rise of the threshold of pain in animals can be depended upon fully. One has to rely on the twitching of muscles, the blinking of eyelids, the withdrawal of certain portions of the body from the

[1] Wolff and Hardy, *Physiol. Revs.*, **27,** 167 (1947).

region of the pain stimulus, or on an outcry of the animal. Even in a series of ten or twenty laboratory animals which show an average susceptibility to a certain test, only an approximate figure of the increase of the pain threshold can be obtained. Moreover, the sensitivity to one and the same stimulus varies from animal to animal, and the same animal will be unable to discriminate between small differences in the intensity of painful stimuli at different occasions. The methods of measuring analgesia deserve a brief discussion because they shed some light on the difficulties of the pharmacological evaluation of analgetic drugs.

II. TESTS FOR ANALGETIC DRUGS

Hesse[2] created pain in the perineal area of mice, or a pressure area in guinea pigs by injection of the irritating croton oil, and used the reaction of the animals as a criterion of pain sensitivity. Not all analgetic drugs respond to these tests. Electric stimulation of the upper incisor of rabbits[3] produces toothache which can be counteracted by oral administration of certain drugs. Only the most potent analgetics such as morphine raise the pain threshold when pain is evoked in rats by an electric current in a cage with a wire bottom.[4] Electric shock is used also to induce pain in the scrotum of rats; the voltage required to cause the animal to squeal is surprisingly constant.[5] In monkeys, pain elicited by an electric current has to be measured by noting a sudden sharp intake of a deep breath.[6]

More widely used is the method of Eddy.[7] It consists of measuring the amount of pressure which will evoke a response when applied to the terminal two inches of a cat's tail. Depending upon the weight and size of the cat, from three to fourteen kilograms of pressure is required. Powerful analgetics such as morphine may raise the threshold to fifty or sixty kilograms. The minimum dose of a drug necessary to show analgesia is taken as a measure of its potency, but as shown in Table I it is not closely related to the initial pressure required to cause a pain reaction in a given series of cats. (See Table I, page 154.)

The advantage of a similar test in mice lies in the large number of animals, and the low cost of the small doses that may be used,[8] but the method is said to be not as accurate as that of Eddy's.

[2] Hesse, *Arch. exptl. Path. Pharmakol.*, **158,** 233 (1930).
[3] Taro Yao, *Chem. Abstr.*, **29,** 2235 (1935). Koll and Reffert, *Arch. exptl. Path. Pharmakol.*, **190,** 687 (1938).
[4] Sivadjian, *Arch. intern. pharmacodynamie*, **52,** 142 (1936).
[5] Macht, D. L., and Macht, M. B., *J. Am. Pharm. Assoc.*, **29,** 193 (1940).
[6] Smith, *J. Pharmacol. Exptl. Therap.*, **62,** 467 (1938).
[7] Eddy, *J. Pharmacol. Exptl. Therap.*, **45,** 343 (1932).
[8] Molitor and Latven, *Anesthesia & Analgesia*, **16,** 127 (1937).

In the method of d'Amour and Smith[9] a strong light is focussed on the tip of a rat's tail. Pain is indicated by a sudden typical switching of that extremity. A similar procedure has been applied by Hardy, Wolff and Goodell[10] in clinical tests for analgesia by focussing the rays of a strong light on the blackened forehead of a test individual. The pain threshold in a large group of patients of different ages and both sexes has been shown to deviate less than one per cent.[11] Similar results have been obtained by Ercoli and Lewis[12] in a radiation method adapted to screening a large number of analgetics in rats.

TABLE I

Initial Pressure, Kg.	After One Hour, Kg.
3.0	6.0
3.0	7.0
3.5	3.5
3.5	6.5
5.0	9.0
7.0	7.0
7.0	11.0

A synopsis of current thought concerning algisimetric methods has been presented in a recent monograph.[13] In addition to the methods recommended in those articles, further proposals[13a] include using contact with an electrically heated wire on the forehead, making the arm ischemic by an inflated cuff, and a method for evaluating analgetics of the anti-arthralgic type in laboratory animals.

The uncertainties of pain conductance, pain blocking and pain reception in the various parts of the nervous system have led to the impression that no compound could be exclusively analgetic, but would invariably exert one or several side effects. Many drugs used as analgetics induce sleep or stupor and may act as hypnotics or as narcotics. It is probable that these compounds (the opiates, Demerol, methadon etc.) do not actually block pain conductance but modify reaction of the individual to the

[9] d'Amour and Smith, *J. Pharmacol. Exptl. Therap.*, **72,** 74 (1941). Compare also Gross, *Helv. Physiol. et Pharmacol. Acta*, **5** (3), C31 (1947).

[10] Hardy, Wolff, and Goodell, *J. Clin. Invest.*, **19,** 649, 659 (1940); **26,** 1152 (1947).

[11] Chapman and Jones, *J. Clin. Invest.*, **23,** 81 (1944). Shumacher, Goodell, Hardy, and Wolff, *Nature*, **92,** 110 (1940).

[12] Ercoli and Lewis, *J. Pharmacol. Exptl. Therap.*, **84,** 301 (1945).

[13] Pfeiffer *et al.*, and L. C. Miller, in "Newer Synthetic Analgesics," *Ann. N. Y. Acad. Sci.*, **51,** 21, 34 (1948).

[13a] Lee, Williams, and Pfeiffer, *Federation Proc.*, **8,** 314 (1949). Hewer and Keele, *Lancet*, **2,** 683 (1948). La Belle and Tislow, *Abstracts*, Indianapolis Meeting, Am. Soc. Pharmacol. Exp. Therapy, 1949, p. 59.

pain by producing a superimposed feeling of well-being (euphoria); the pain persists but becomes a matter of indifference to the afflicted animal or patient. In addition to producing euphoria, some of these compounds are also potent antispasmodics.

Other analgetics have the ability of lowering the body temperature in fever, and are classifiable as antipyretics. It has been claimed that this is due to some overlapping of neural structures controlling maintenance of temperature and pain reception in the central organs, but some neurologists feel there is probably no such relation.

The most effective analgetics discovered so far possess uniformly a stimulating effect which is observable prior to relief from pain. This undesirable central stimulation may take the course of a defense reaction against depression but it may also induce euphoria (well feeling) and thereby lead to a desire to repeat this effect by successive administrations of the drug, if necessary in increased doses. From a medicinal point of view, euphoria is desirable if the patient is to be put in a calm and unapprehensive state of mind, particularly in preparation for surgery. It is thought of as an objectionable side action of analgetics if the patient becomes habituated or addicted to the drug and, at least in the case of morphine and its structural analogs, may not be able to break this dependence without very serious withdrawal symptoms.

The analgetics are cell depressants and frequently alter nervous functions whose physiological course should not be affected. The inhibition of peristalsis by morphine and the stimulation of respiration by heroin are examples of such effects. If a beneficial side action becomes preponderant, as the action of codeine on the cough reflex, it may be useful in medical practice. But on the whole, the search for an ideal analgetic has as its aim the production of a compound which raises the pain threshold through a central mechanism, and exhibits no other activity.

The difficulty of evaluating analgetic activity is expressed also in the inaccuracy or lack of information contained in most of the older publications on this subject. It is more the rule than the exception that a large number of compounds has been prepared for the purpose of analgetic testing and, if the activity is given at all, it is only mentioned that the compound has been found to be active, moderately active, very active, almost inactive etc. If the compound has been found to be virtually inactive, a repetition of the experiment may seem useless, but many valuable drugs which when administered under controlled conditions may show up favorably in the more modern tests have probably been discarded in the older literature. In the Tables incorporated in this chapter, plus and minus signs have been used to cope with some of these statements. For moderately active com-

TABLE II. ACTIVITY OF SOME ANALGETICS

Drug	Test Method (Reference)	Analgetic Dose, mg./kg. Ineffective	Analgetic Dose, mg./kg. Effective	Lethal Dose mg.	Therapeutic Dose grams	Duration of Action, Hours	Maximum Rise of Pain Threshold, %
Morphine sulfate	Rats (9)		12		0.03	6	100
	Rats (5)		1				
Morphine·HCl	Cats (7)	0.5	1	500–700		5	
	Mice (2)	50 (oral)	100 (oral)	800 (oral)			
Heroin					0.0015	2–3	110
Dilaudid					0.002	3–4	110
Methadon					0.0025	3–4	100
Metopon					0.005	3–4	100
Codeine					0.06	2–3	48
Demerol					0.1	2–3	50
Antipyrine	Rats (5)		10				
	Mice (2)		1000 (oral)	1300 (oral)			
Aminopyrine	Rats (5)						
	Mice (2)	200 (oral)	30–300 (oral)				
Acetanilide	Rats (5)		4		0.5	2	30
	Mice (2)	800 (oral)		1400 (oral)			
Acetophenetidine	Rats (5)		30 (oral)		0.5	2	35
	Mice (2)		1300 (oral)	2000 (oral)			
Sodium Salicylate	Rats (5)		10 (oral)				
Aspirin	Rats (5)		30 (oral)		2.0	2	35
	Mice (2)	1400 (oral)	1600 (oral)				
Paraldehyde					10	2–3	20

pounds one plus sign is shown. Two plus signs stand for great or excellent activity, while a minus sign may mean virtually no activity, or no activity at all. The difference of evaluation resulting from various testing methods is illustrated in Table II. The test procedures of Macht[5] and of Eddy[7] determine the amount of drug required to raise the pain threshold by a very slight amount. If as in Hesse's method[2] the dose required to overcome a very painful stimulus is measured, a much larger dose will be required than in the previous tests. Total analgesia, that means complete freedom from pain even under attenuating conditions, is measured in the method of d'Amour and Smith[9] and, consequently, this method is a much more stringent one.

III. MORPHINE AND THE OPIATES

1. Opium Alkaloids

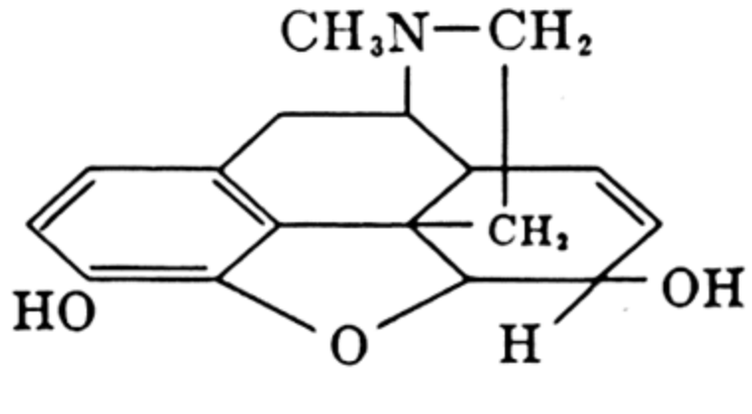
Opium is the sun-dried latex from the unripe fruit of *Papaver somniferum*, twenty per cent of which consists of alkaloids. Because of the supreme pain-relieving action of some of these alkaloids and their derivatives (the opiates), the production of opium is very large; unfortunately, the euphoric action of opium and some opiates channels an undue percentage of this production into the illegal narcotic trade.

The opium poppy is cultivated in China, Persia, India, Egypt and particularly in Asia-Minor. The gummy, dark exudate of the sun-dried capsules is powdered, deodorized and processed into the so-called officinal powdered or granular opium. Opium contains approximately twenty-three alkaloids besides gums, sugars, organic acids, resins, proteins and other materials. A mixture of the purified total alkaloids is widely used by physicians because of the possibility of getting the overall pharmacological effect of opium from these substances rather than the effect of one individual component. One preparation of the total alkaloids of opium in the form of their hydrochlorides has become known as Pantopon.

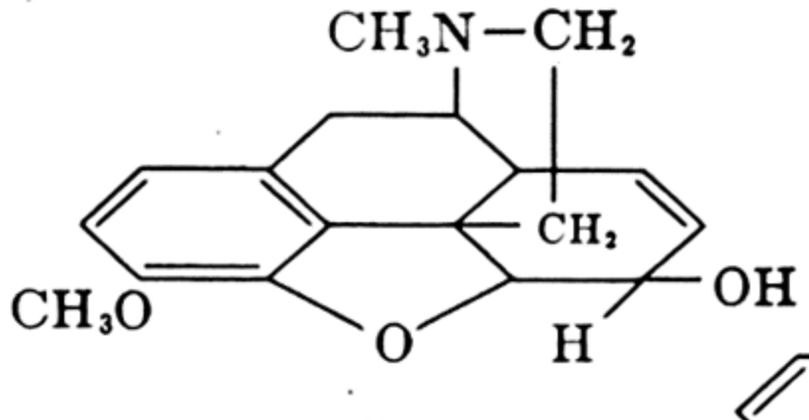
There are two different principal types of opium alkaloids, those containing the phenanthrene nucleus including morphine, codeine and thebaine which act primarily on the central nervous system and produce depressant and stimulating effects as well as contraction of the smooth muscles, and the other type, derivatives of 1-benzylisoquinoline. The best known representatives of this group are narcotine and papaverine which have little action on the central nervous system. Papaverine, however, has been used extensively to relieve spasms of smooth muscles (see Chapter XXIII). The most important opium alkaloids and their structural formulas are tabulated below. They are morphine (XI-1; 9%); codeine (XI-2; 0.3%); thebaine (XI-3; 0.4%); narcotine (XI-4; 5%); papaverine (XI-5;

0.8%); laudanine (XI-6; 0.01%); cryptopine (XI-7; 0.08%); protopine (XI-8; 0.003%); narceine (XI-9; 0.2%). The percentage figures refer to the average amounts of the bases occurring in opium.

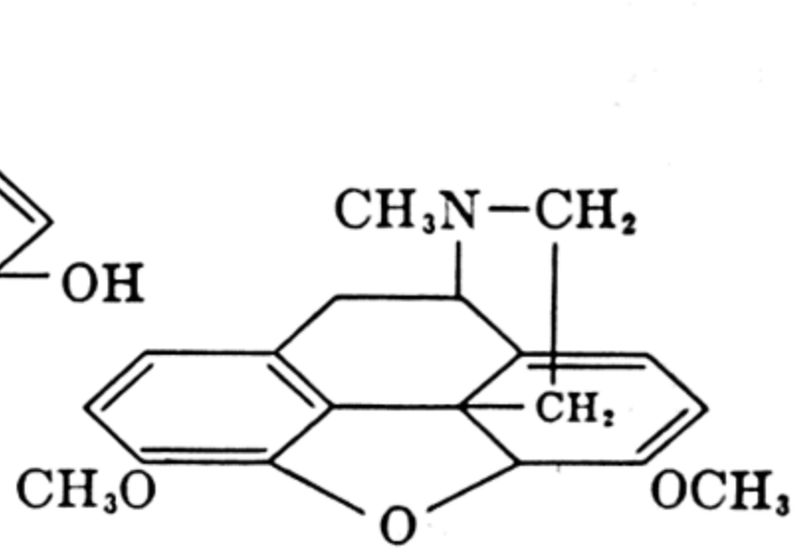
TABLE III. THE PRINCIPAL OPIUM ALKALOIDS



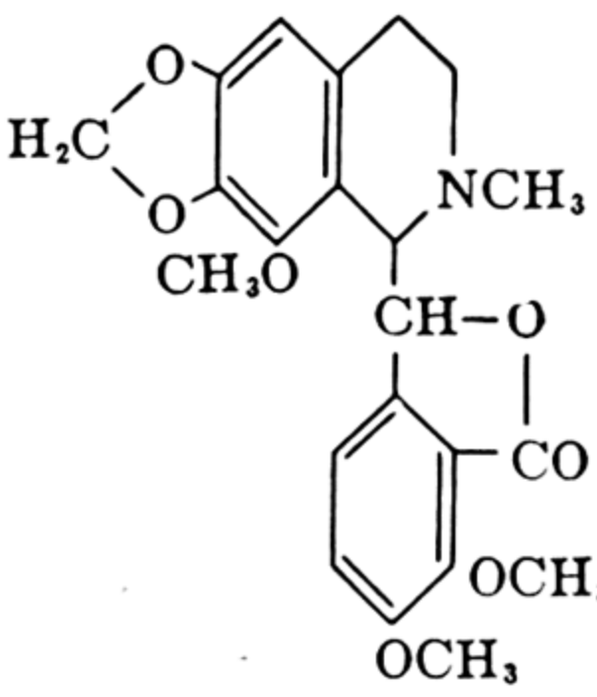
(XI-1)



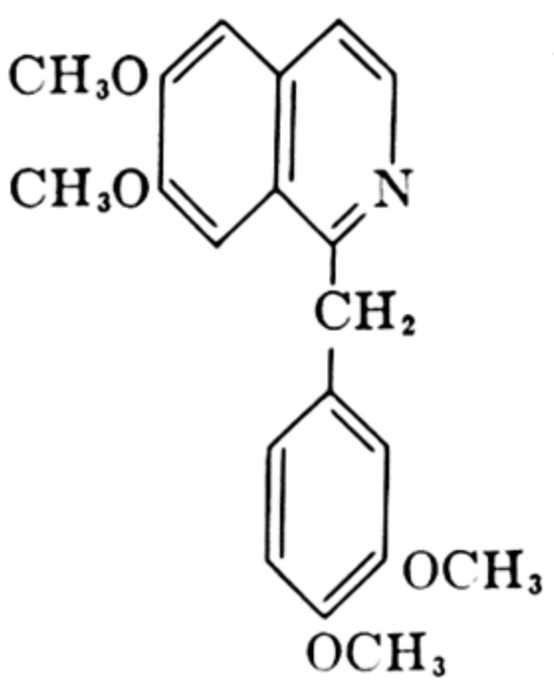
(XI-2)



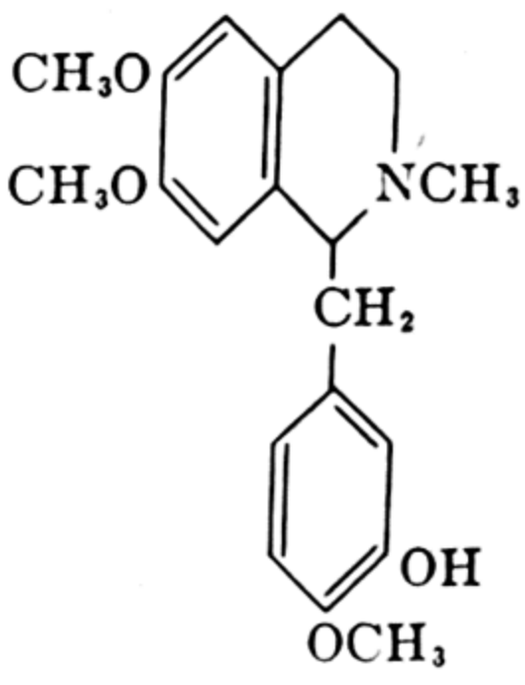
(XI-3)



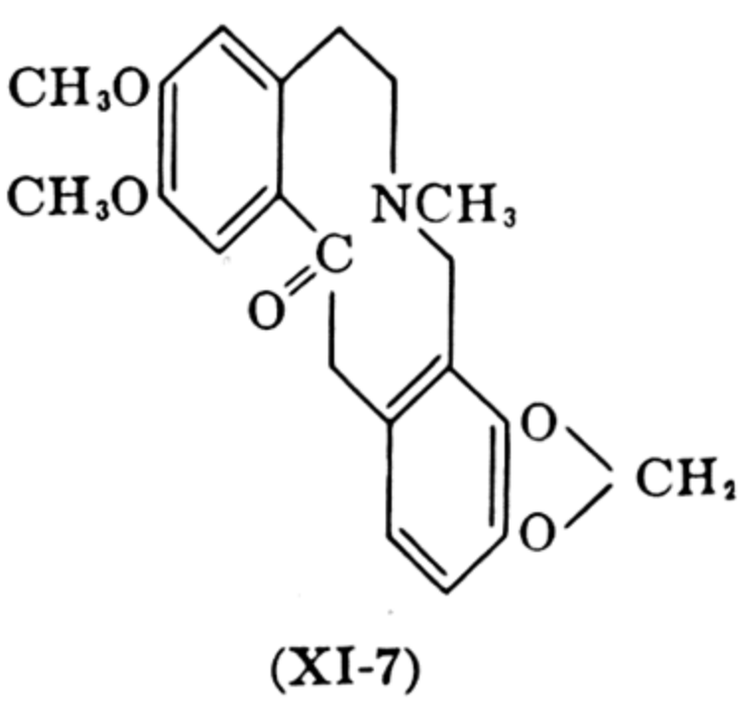
(XI-4)



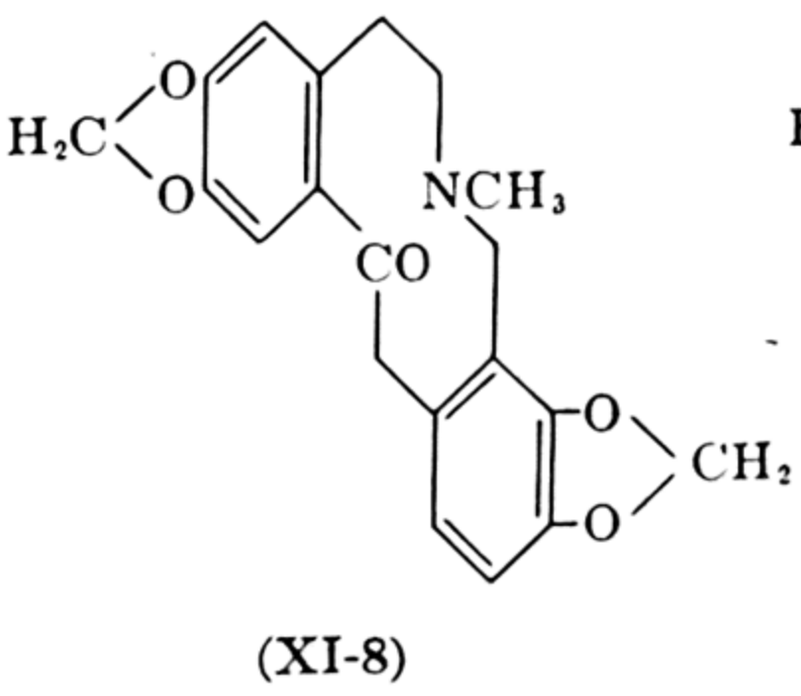
(XI-5)



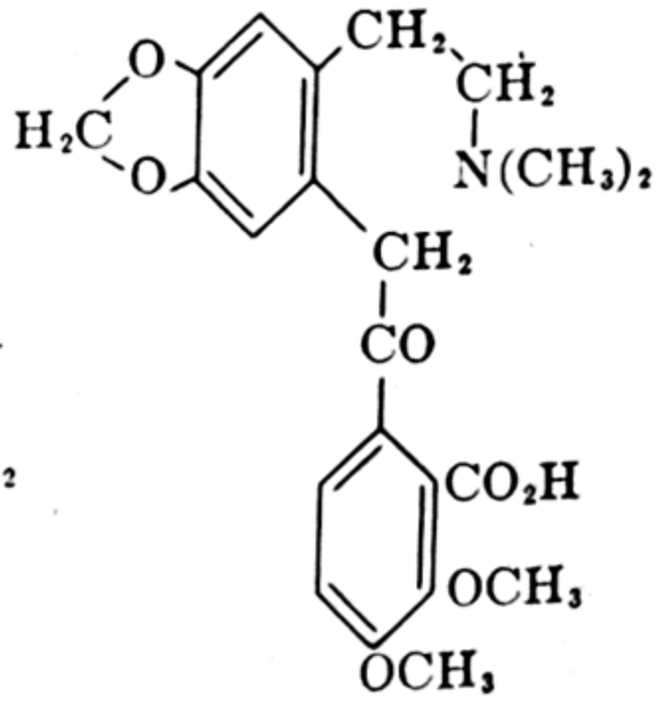
(XI-6)



(XI-7)



(XI-8)



(XI-9)

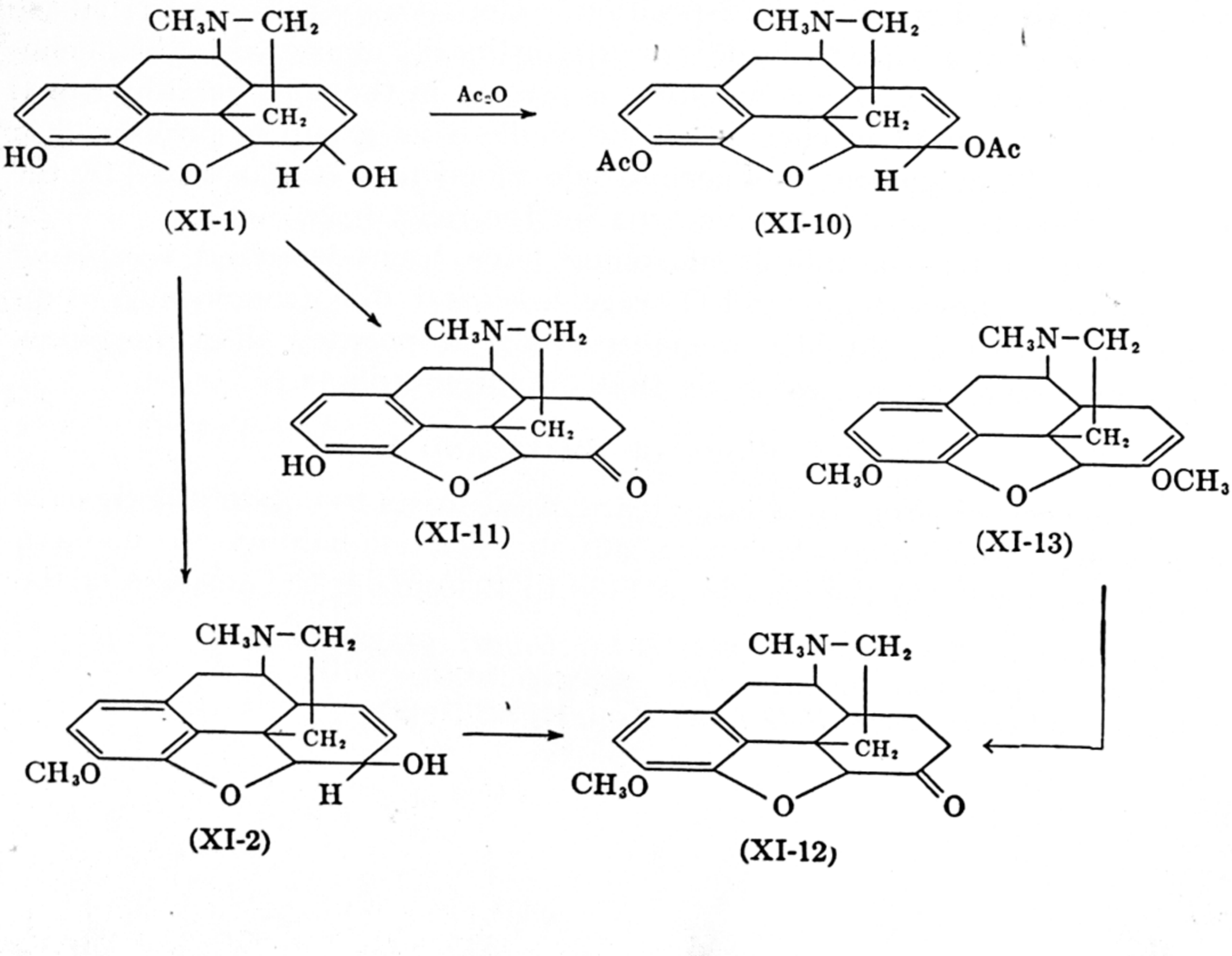
(Following the discovery of the analgetic activity of the main opium alkaloid, morphine, not only its pleasurable euphoric effect but also other medically undesirable side-actions became known. They are briefly, mani-

festations on the respiratory and circulatory systems, the gastro-intestinal tract, emetic and general depressant symptoms. The latter, induction of stupor and deep sleep, may be auxiliary rather than objectionable to analgesia in the case of opiates. While these side-actions may be overlooked in view of the excellent analgetic effect of morphine, the most serious drawback of its administration is still its addiction liability.

2. Structural Variations

As soon as the relation of the less strongly addicting and analgetic alkaloid codeine (XI-2) to morphine was recognized it became apparent that not only the pharmacologically desirable properties of morphine, but also the development of dependence after prolonged administration seems to be related to the presence of certain peripheral groups of the morphine skeleton which might well be modified by chemical processes. This hope, together with the desire to eliminate other undesirable side-actions of the alkaloid have prompted generations of chemists to synthesize derivatives of morphine which would have only its desirable pharmacological effects. In addition, these compounds should have a lower toxicity since morphine does not show an all-too great margin of safety, its therapeutic index in adults being about 1:6.

The difficulties attending these researches are demonstrated by the fact that replacement of the N-methyl group of morphine by N-allyl produces an excellent morphine *antagonist.*

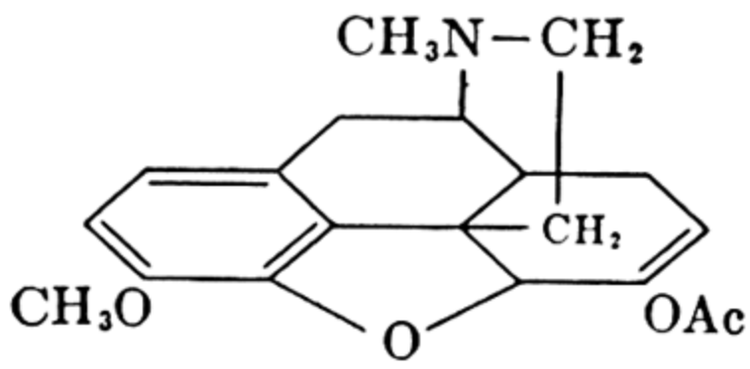


(XI-1) (XI-10) (XI-11) (XI-13) (XI-2) (XI-12)

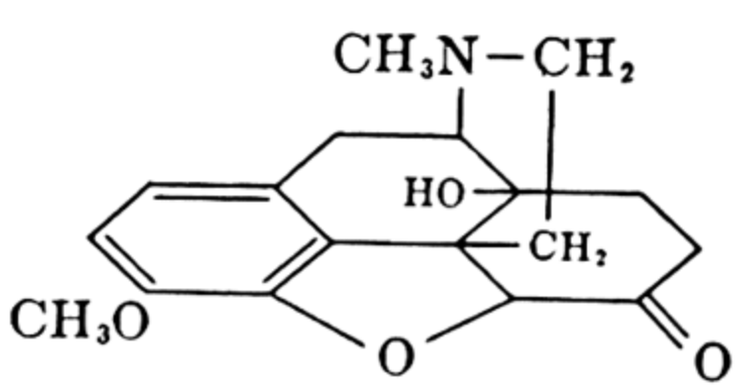
a. Dilaudid, Dicodid, Eucodal

(Early modifications of the morphine molecule included diacetyl morphine (heroin, XI-10) which shows a considerably higher analgetic action than the parent compound, but its euphoric and respiratory effects are so prominent that it has fallen in disrepute. Dihydromorphinone (Dilaudid, XI-11) prepared by catalytic rearrangement of morphine,[14] as well as its methyl ether, dihydrocodeinone (Dicodid, XI-12) prepared by a similar rearrangement of codeine or by hydrolysis of dihydrothebaine (XI-13), the methyl enolate of dihydrocodeinone,[15] have been used successfully as substitutes for morphine.)

In the study of the series culminating in the introduction of Dilaudid and Dicodid it was observed that the morphine derivatives with the most useful range of activity contain a free phenolic hydroxyl group in position 3. Exceptions to this rule are Acedicon (acetyldemethyldihydrothebaine, XI-14) and eucodal (dihydrohydroxycodeinone, XI-15) both of which



(XI-14)



(XI-15)

carry a methoxyl group in the 3-position. Here it may be assumed that the natural balance of basic and acidic groups ordinarily expressed in the phenolic hydroxyl of the active compounds is present in the additional hydroxyl group in position 14 in eucodal or the enolic ester group in position 6 in Acedicon. The significance of certain side-effects may be illustrated by the use of Dicodid as an antitussive drug for the relief from cough.

Soluble esters of dihydromorphine have been described recently.[16] Glycyl dihydromorphine, and O-acetyl-L-tyrosyl dihydromorphine combine with greater solubility a higher analgetic potency than morphine. They are, however, no less toxic that dihydromorphine.

b. The Work of Small and Eddy

A concerted effort by a large team of scientists to obtain a derivative of morphine which might lack especially its addiction liability was made in the United States in the decade of 1930 to 1940 under the auspices of the

[14] Knoll and Co., Germ. Pats. 365,683; 380,919; 607,931; 617,283; 623,821.
[15] Freund, Speyer, and Guttmann, *Ber.*, **53,** 2250 (1920).
[16] Karrer and Heynemann, *Helv. Chim. Acta*, **31,** 398 (1948).

Committee on Drug Addiction of the National Research Council. Largely through the work of Small and of Eddy approximately 125 morphine derivatives were synthesized and tested for analgetic and other pharmocological properties. Toxicity in mice, convulsant action in mice, general depressant effects in rats, analgesia in cats, exciting effects in cats, emetic action in cats, and respiratory effects in rabbits were compared. In many cases other phenomena such as the action on the gastro-intestinal tract were also studied.

The results of this vast experimental work have been summarized in a monograph.[17] The general conclusions were that muzzling of the phenolic hydroxyl group in morphine or any related compound by etherification or by esterification almost always increases convulsant action and decreases all other morphine-like effects, while blocking of the alcoholic hydroxyl by the same processes, by oxidation to a ketonic group, or by reduction, or by replacement with halogen not only generally increases the toxicity and convulsant action of the drug, but also has a tendency to increase other morphine-like effects. A shift of the alcoholic hydroxyl group from position 6 into 8 generally results in a decrease of pharmacological action, but a spatial reversal of the groups in position 6 from the morphine or codeine types to the α-isomorphine or isocodeine configuration generally leads to an increase in activity.

The opening of the ether bridge in morphine seems to decrease activity. Substitution in the aromatic nucleus, and saturation of the 7,8- or 6,7-double bonds in the morphine series causes unpredictable changes of the generally decreased physiological effects in the resulting products.

Metopon

Nuclear substitution by alkyl groups in the isocyclic ring of morphine may increase or decrease the effect of the latter. However, in two alkyl derivatives, methyldihydromorphinone (Metopon, XI-16), and 6-methyldihydromorphine (XI-20) the increased activity of the compound is not accompanied by a corresponding decrease of the duration of the action, and thus a dissociation of analgetic activity and of dependence formation has been achieved. Pharmacological and clinical studies of Metopon[18] have revealed that it is relatively free from nauseating effects and does not produce mental dullness. It affords adequate relief of chronic deep-seated

[17] Small, Eddy, Mosettig, and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, U. S. Govt. Printing Office, Washington, 1938.

[18] Eddy, N. B., in "Newer Synthetic Analgesics," *Ann. N. Y. Acad. Sci.*, **51,** 51 (1948).

pain by oral administration and has been introduced for analgesia in inoperable terminal neoplastic disease. Tolerance to Metopon and addiction develop slowly. Its main disadvantage is the difficulty of its preparation.

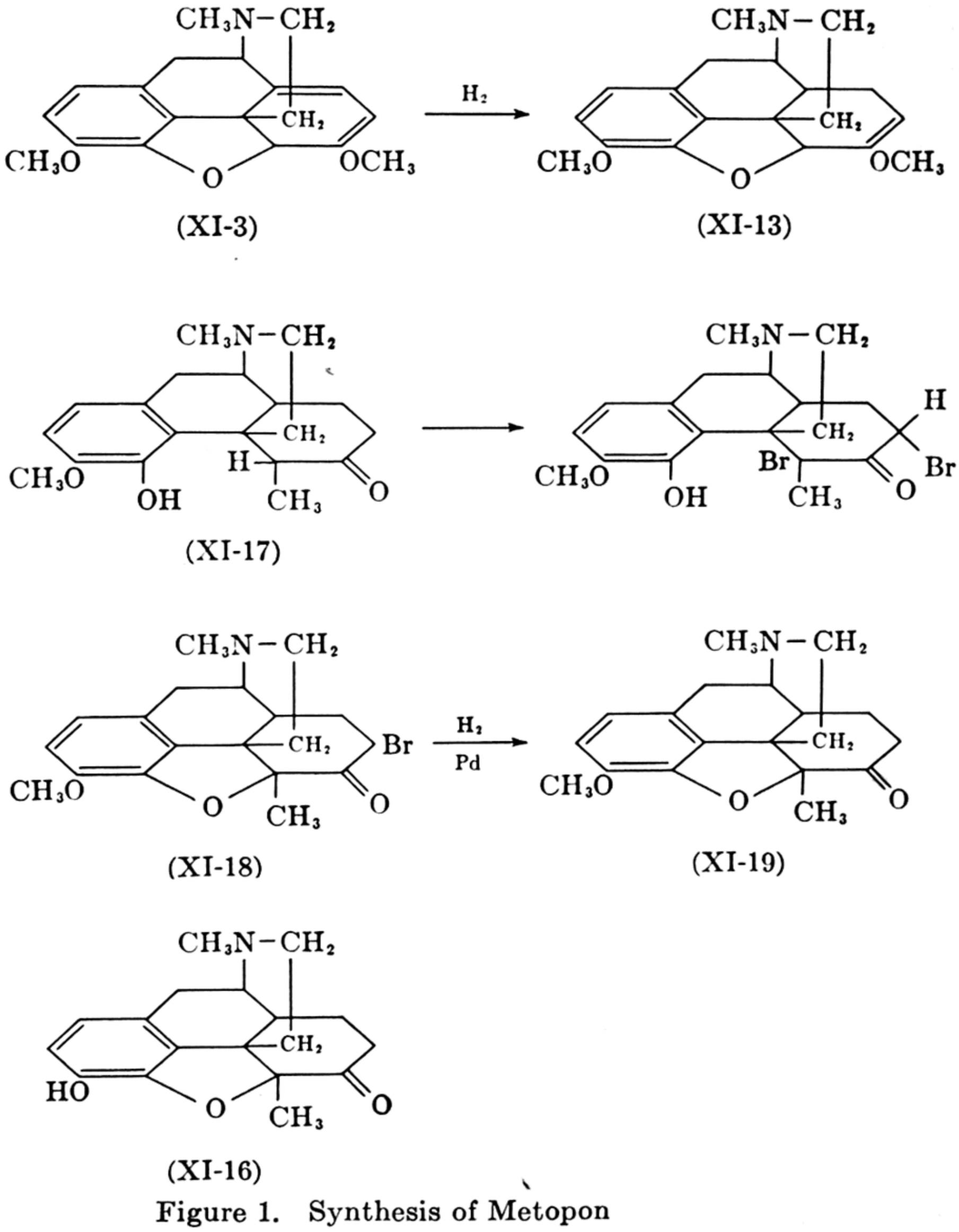


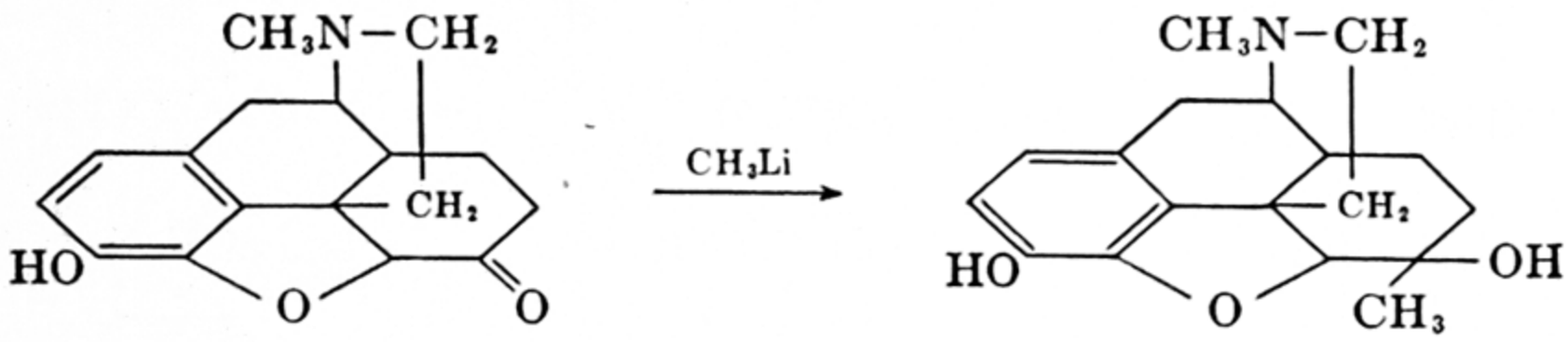
Figure 1. Synthesis of Metopon

The synthesis by Small, Fitch and Smith[19] utilizes the reaction of the enol ethers or enol esters of morphine type ketones with Grignard reagents. An alkyl group is introduced at C^5, or perhaps at C^7 by an 1,2- or 1,4-

[19] Small, Fitch, and Smith, *J. Am. Chem. Soc.*, **58,** 1457 (1936).

addition of the Grignard reagent (XI-17), and the furan ring is opened with simultaneous hydrolysis of the enol ether or ester group. The oxide ring is closed subsequently by bromination (XI-18) and elimination of hydrogen bromide (XI-18, 19). The methoxyl group is finally hydrolyzed by the action of hydrobromic acid (XI-19, 16).

It is interesting that the Grignard reagent does not attack the keto group of 5-methyldihydrothebainone, but the morphine ketones are known for their refractory behavior against alkylmagnesium halides. This does not hold, however, for their reactions with organolithium compounds. For example, dihydromorphinone (XI-11) reacts with two moles of methyllithium to give 6-methyldihydromorphine (XI-20) which has been shown to possess prolonged analgetic action.[20]

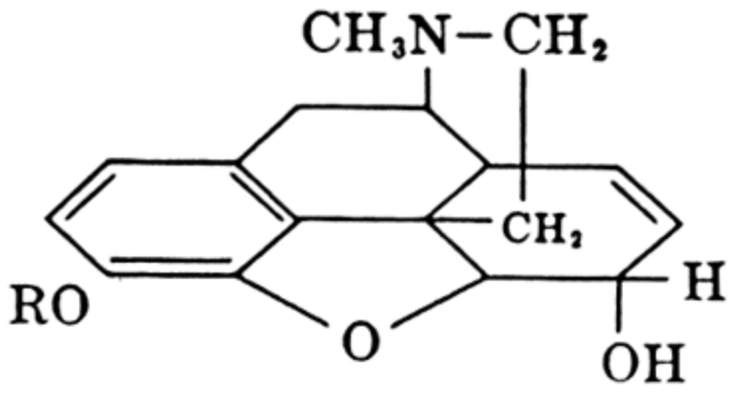


(XI-11) (XI-20)

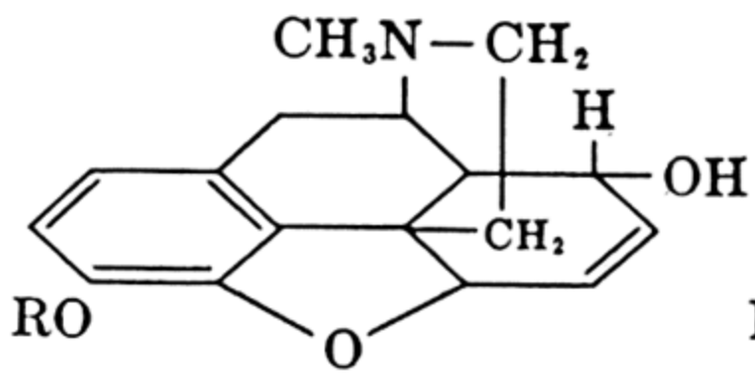
Depending on the conditions used, the hydrogenation of the halogen analogs of the morphine series, the chloro- or bromomorphides, may yield almost entirely the so-called dihydrodesoxymorphine types, or it may lead to tetrahydrodesoxymorphine. Dihydrodesoxymorphine D (Desomorphine) has been shown to be an analgetic about nine times stronger than morphine. Particularly remarkable is the almost total lack of emetic and other effects of this drug on the gastro-intestinal tract.

In Table IV, pharmacological data of some of the compounds discussed in the preceding paragraphs are listed. The structural formulas of those morphine derivatives not previously pictured are grouped in Figure 2. All data are from Studies on Drug Addiction,[17] and the headings are interpreted as follows:
Toxicity, administered subcutaneously to mice.
Convulsant Action, the smallest dose causing convulsions in mice.
Analgesia: Minimum dose administered intramuscularly which caused in at least four of five cats a response in the Eddy pressure test.
Exciting Effect: Minimum dose causing excitement in at least two of five cats.
Emetic Action: Minimum dose causing nausea, licking or vomiting in cats.
General Depression: Smallest dose preventing immediate righting of at least 15 of 20 rats, one-half hour after intraperitoneal administration.
Respiratory Effect: As defined by Wright and Barbor.[21]

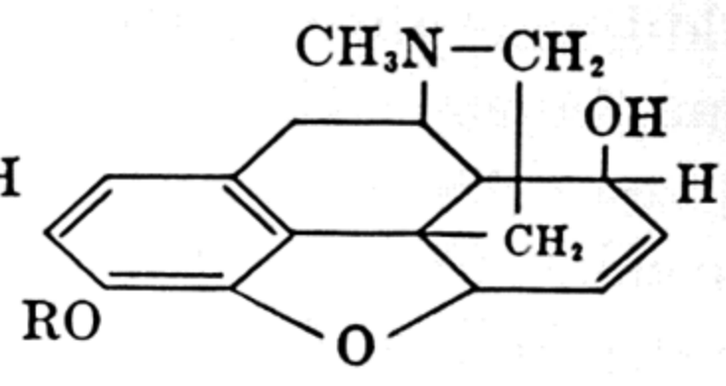
[20] Small and Rappaport, *J. Org. Chem.*, **12,** 284 (1947).
[21] Wright and Barbour, *J. Pharmacol. Exptl. Therap.*, **61,** 422 (1937).



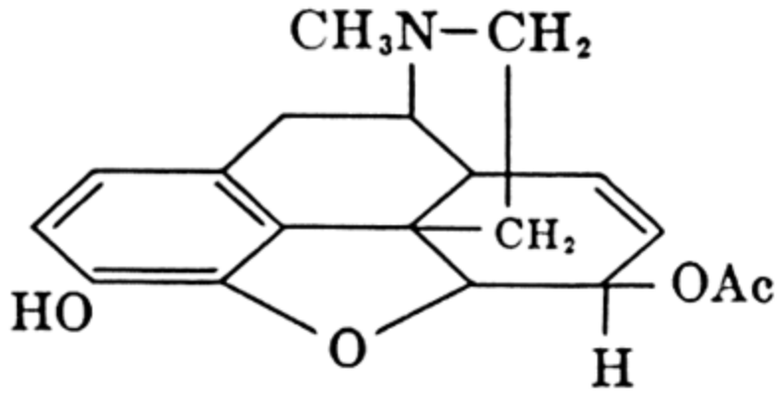
(XI-21) : R=H
(XI-22) : R=CH_3



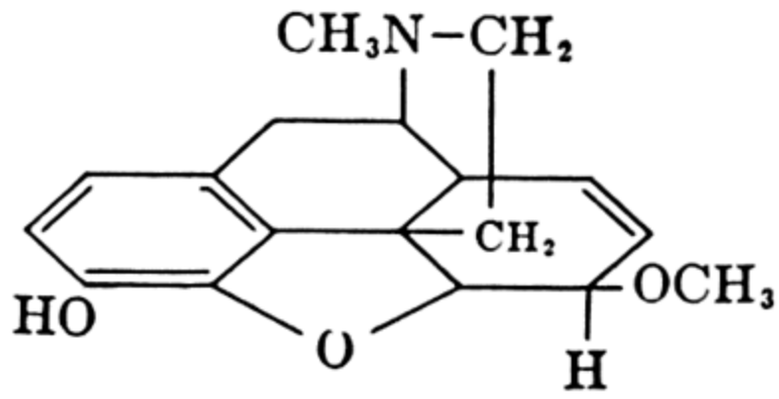
(XI-23) : R=H
(XI-24) : R=CH_3



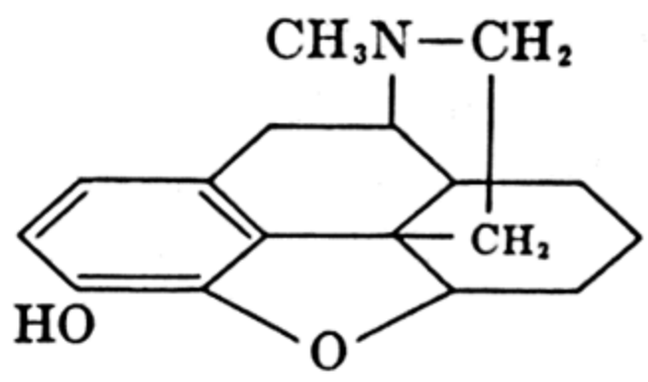
(XI-25) : R=H
(XI-26) : R=CH_3



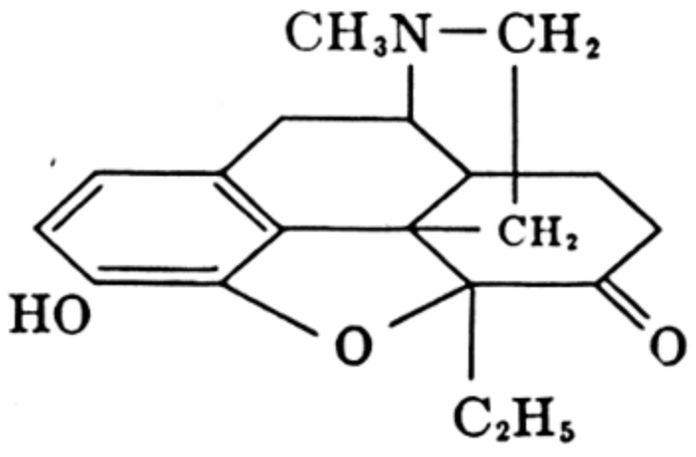
(XI-27)



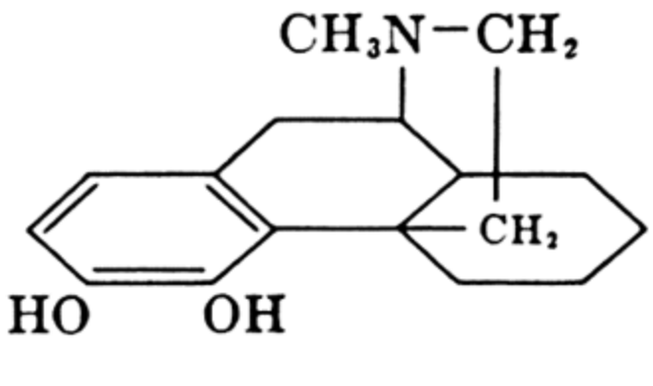
(XI-28)



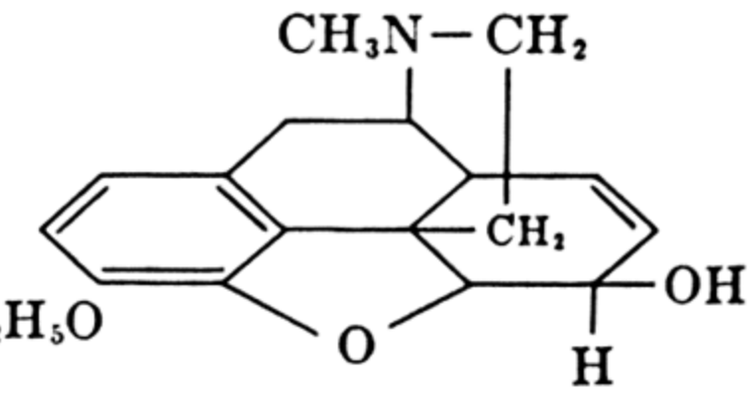
(XI-29)



(XI-31)



(XI-30)



(XI-32)

Figure 2. Structures of Some Morphine Derivatives

TABLE IV. PHARMACOLOGICAL EFFECT OF SOME MORPHINE DERIVATIVES[17]

Alkaloidal Base	Formula No. XI-n	LD50, mg./kg.	Convulsant Action mg./kg.	Analgesia mg./kg.	Exciting Effect mg./kg.	Emetic Action mg./kg.	General Depression mg./kg.	Respiratory Effects mg./kg.
Morphine	-1	531	531	0.75	0.57	0.22	6.75	0.15
Codeine	-2	241	161	8.04	8.04	16.0+	36.1	1.3
Ethylmorphine (Dionine)	-32	136	122	7.66	17.0	8.5+	42.6	0.48
α-Isomorphine	-21	890		0.80	0.89	0.13	22.2	0.15
Isocodeine	-22	589	589	13.0	13.0		58.9	
β-Isomorphine	-23	324	324	10.1	9.26	4.63	74.0	2.14
Allopseudocodeine	-24	267	178	13.3	26.7	13.3+	80.1	
γ-Isomorphine	-25	2000+		7.09	7.09	1.77	133+	2.36
Pseudocodeine	-26	1780		17.8	22.2	4.45	89.1	48.0
Monoacetylmorphine	-27	293	180	0.18	0.18	0.18+	0.9	

Table continued

TABLE IV (*Continued*)

Alkaloidal Base	Formula No. XI-n	LD50, mg./kg.	Convulsant Action mg./kg.	Analgesia mg./kg.	Exciting Effect mg./kg.	Emetic Action mg./kg.	General Depression mg./kg.	Respiratory Effects. mg./kg
Heterocodeine	-28	72	65	0.48	0.32	2.40+	1.40	0.016
Dihydromorphinone (Dilaudid)	-11	84	67	0.17	0.17	0.08	0.88	0.011
Dihydrocodeinone (Dicodid)	-12	86	47	1.28	0.86	2.56+	4.20	0.08
Dihydrodesoxymorphine-D (Desomorphine)	-29	104	104	0.08	0.16	low	0.32	0.012
Tetrahydro desoxymorphine	-30	221		0.62	1.86	6.20+	14.0	
Methyldihydromorphinone (Metopone)	-16	25	25	0.07	0.10	0.07	3.00	0.012
Ethyldihydromorphinone	-31	27	22	0.17	0.09	0.17	2.01	0.021
Dihydrohydroxycodeinone (Eucodal)	-15	426	426	1.34	0.89	0.89+	1.34	0.10

3. Hypotheses Concerning the Mode of Action of Morphine

Clues as to the cause of the analgetic activity of morphine have been sought in a study of its action on isolated enzymes. Perhaps the most noteworthy relation in this field is the strong inhibition of cholinesterase by morphine.[22]

Cholinesterase is an enzyme which catalyzes the hydrolysis of the parasympathetic mediator, acetylcholine, to acetic acid and choline. If morphine is present in the brain, the hydrolysis of acetylcholine by the now inhibited cholinesterase is blocked.

It has been pointed out that morphine may not really interrupt pain conductance but only modify the individual's attitude towards pain by superimposing on pain reception a feeling of euphoria. The biochemical mechanism of this superimposition is not clear. Pero[23] has advanced the

[22] Bernheim and Bernheim, *J. Pharmacol. Exptl. Therap.*, **57,** 427 (1936).
[23] Pero, *Giornale ital. anestesia e analgesia*, **5,** 128 (1939).

hypothesis that analgesia is an adrenergic process, that is, it stimulates the secretion of epinephrine (or its precursor, norepinephrine) at the synapses.

However, a discharge of epinephrine from the adrenal medulla upon administration of morphine has been observed and may, in part, explain the analgetic action of the opium alkaloid.[24] Since the discharge of epinephrine by the gland is known to be a cholinergic phenomenon (Chapter XIX), a unification of the fundamental views of morphine activity does not appear to have been reached as yet. The drop in blood pressure observed after injection of morphine points to a cholinergic component of the action of the alkaloid. On the other hand, the analgetic effects of epinephrine, ephedrine, and other sympathomimetic amines (Chapter XIX) make it appear that pain is a cholinergic phenomenon, i.e., connected with parasympathetic stimulation.

Euphoria is essentially a form of stimulation of the central nervous system and is not necessarily related biochemically to adrenergic activity. It is quite likely that different enzyme systems are concerned with the pleasing stimulation of the intellectual centers, and with the increase of blood pressure and vasoconstriction. Such a separation of action can also be seen in amphetamine which produces both sets of effects (Chapter XIX).

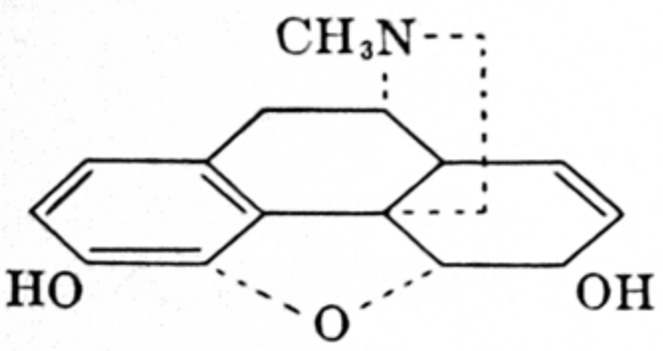
Dependence on morphine is developed in an individual according to his physical and mental qualities after a number of administrations, and begins usually with tolerance of the drug. With an increase of the dosage he acquires the strong desire to repeat the euphoric action brought about by morphine. After addiction is established, the patient experiences, upon withdrawal, symptoms characterized by severe physiological reactions. No satisfactory explanation for the withdrawal symptoms and their ultimate disappearance, that is, return to normal physiological conditions has been offered.[25] It is interesting that in an addict receiving enough morphine to keep him in undisturbed addiction balance, an injection of physostigmine, a powerful inhibitor of cholinesterase (Chapter XXI) brings about withdrawal symptoms. Whether this can be interpreted as a protection of brain cholinesterase from the inhibitory effects of morphine, or as a more far-reaching upset of enzyme balance will have to be determined by further studies. Other lines of thought have centered around a hypothetical antimorphine factor (histamine?) which might be responsible for the abstinence syndrome. This idea is based on the observation that Pyribenzamine can be used as an adjunct in the control of morphine withdrawal symptoms.[26]

[24] Puharich and Goetzl, *Permanente Found. Bull.*, **5,** 19 (1947).
[25] Seevers, Isbell, and Batterman, in "Newer Synthetic Analgesics," *Ann. N. Y. Acad. Sci.*, **51,** 98, 108, 123 (1948).
[26] Kells, *Southern Med. J.*, **41,** 134 (1948).

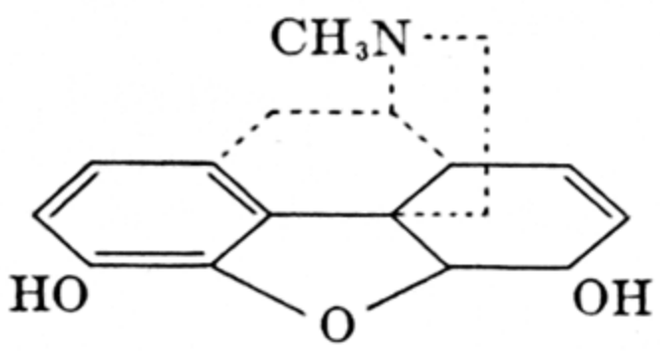
IV. SYNTHETIC ANALGETICS[27]

1. Derivatives of Phenanthrene and Related Ring Systems

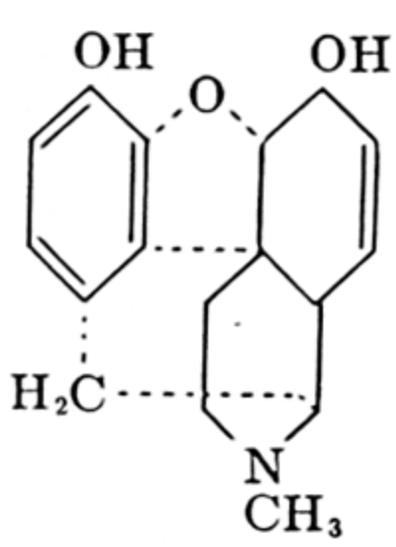
It has always been an intriguing problem to the organic chemist to find out which of the structural components of a naturally occurring physiologically active compound are responsible for its pharmacological behavior. In the case of morphine, the task is particularly difficult since we can discern in the molecule of this alkaloid a variety of structural features. Morphine (XI-1) may be regarded as a derivative of (a) phenanthrene, (b) dibenzofuran, (c) isoquinoline, (d) piperidine, (e) benzodihydrofuran, (f) furan and a number of other ring systems. While a few attempts to synthesize derivatives of some of these ring systems had been recorded earlier, several hundred derivatives of phenanthrene and its hydrogenated derivatives, as well



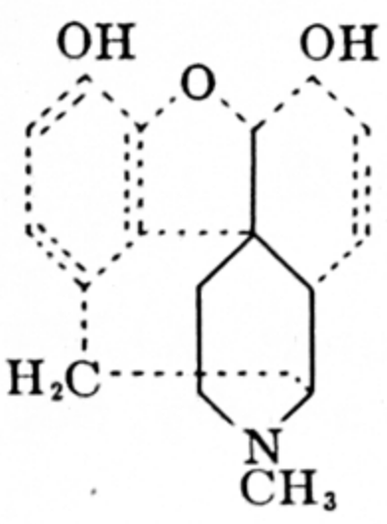
(XI-1a)



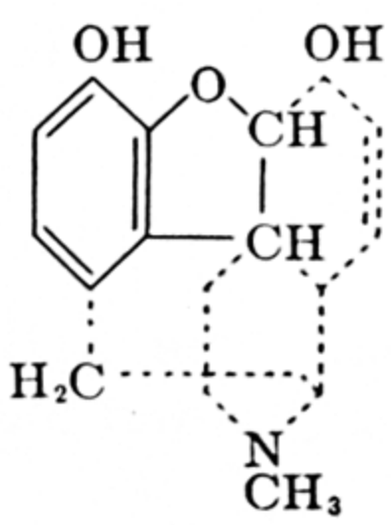
(XI-1b)



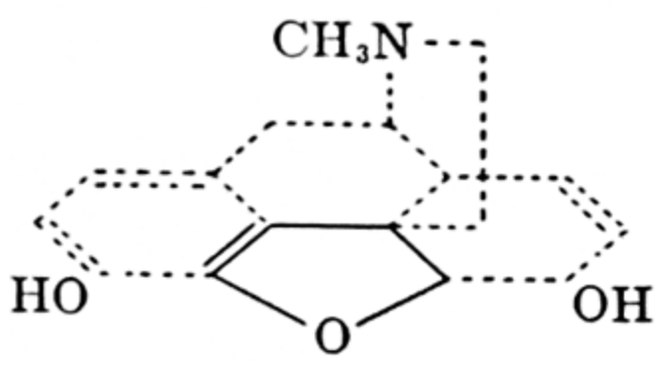
(XI-1c)



(XI-1d)



(XI-1e)



(XI-1f)

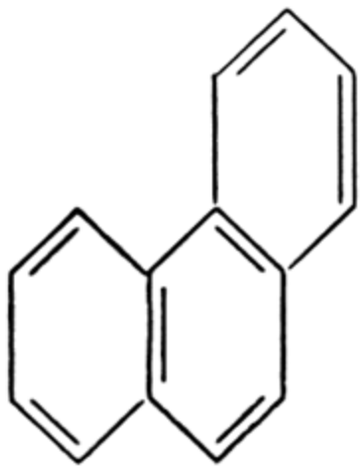
as of dibenzofuran, carbazole, dibenzothiophene, and of benzodihydrofuran were tested between 1930 and 1945.

A few general conclusions of these researches can be drawn. The action of the very weakly depressant hydrocarbons phenanthrene, 9,10-dihydrophenanthrene, 1,2,3,4-tetrahydrophenanthrene, and octahydrophenanthrene may be enhanced to the point of endowing them with analgetic activity by the addition of simple substituents such as hydroxyl and amino groups. In most cases the 3- derivatives are more active than the 2- or 9- derivatives. Disubstitution of the phenanthrene nucleus or muzzling of various simple substituents such as acetylation of hydroxyl or amino

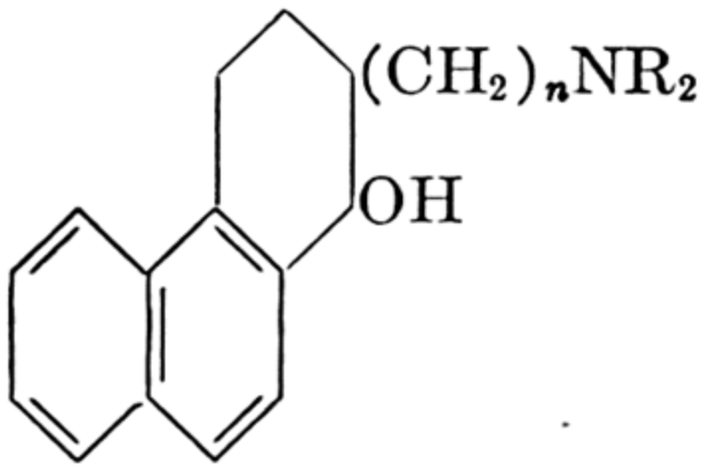
[27] Recent Reviews: Small, in "Newer Synthetic Analgesics," *Ann. N. Y. Acad. Sci.*, **51,** 12 (1948). Bergel and Morrison, *Quart. Rev. Chem. Soc.*, **2,** 349 (1948).

groups, or esterification of carboxyl groups usually leads to a decrease of activity. In all cases the 9- substituted derivatives have shown a curare or veratrine-type delayed relaxation.

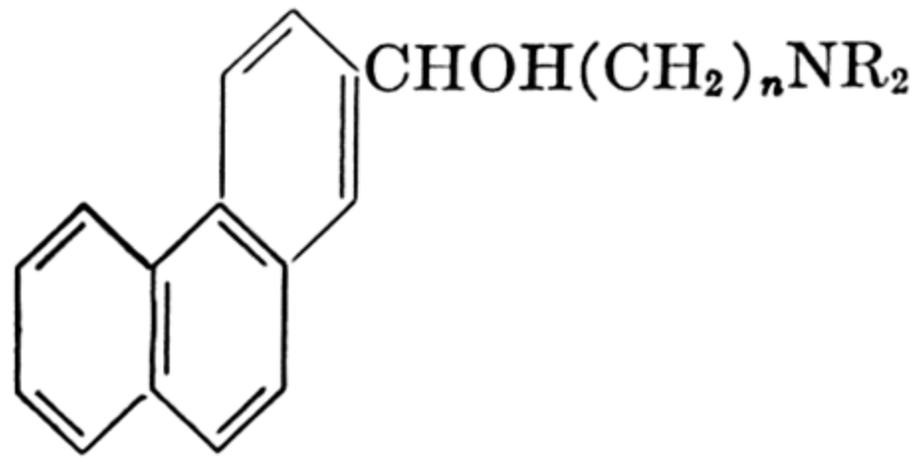
The most important derivatives to exhibit analgetic activity were amino alcohols of types (XI-33, 34, and 35). Amino alcohols with an activity approaching that of codeine were found in the tetrahydrophenanthrene series when both the alcoholic hydroxyl and the tertiary amino group



(XI-33)

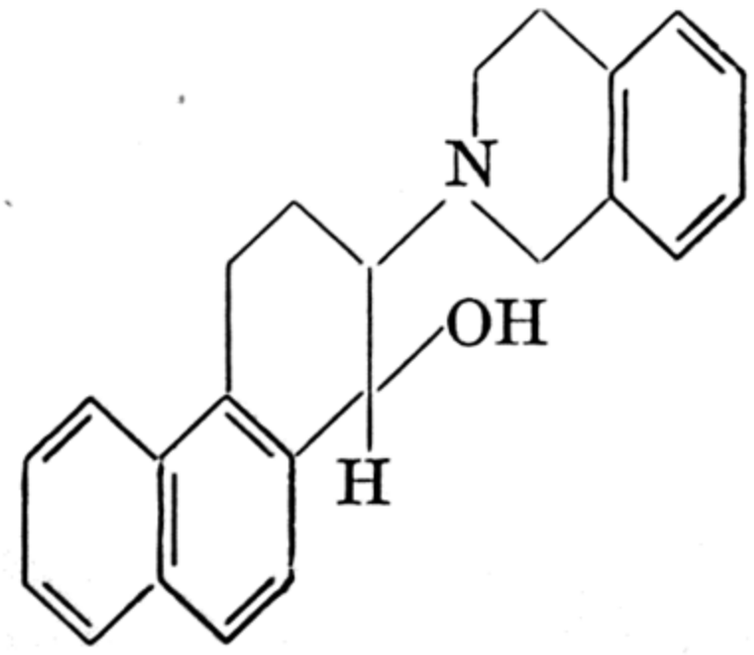


$n = 0$ or 1
(XI-34)

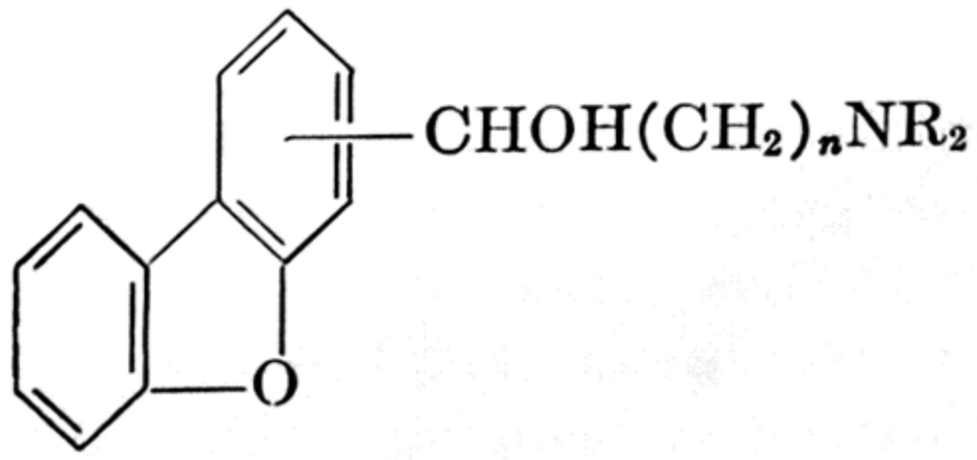


$n = 1$ or 2
(XI-35)

were a part of the hydrogenated ring. One of these compounds (XI-36) not only possessed a relatively low toxicity and high analgetic activity, but



(XI-36)

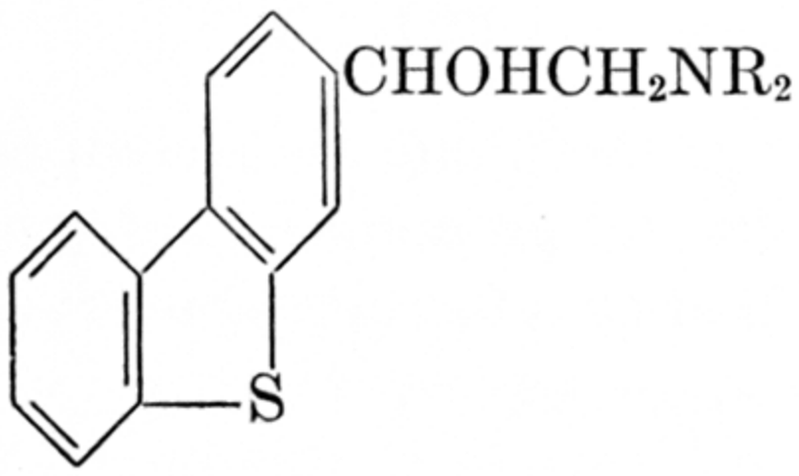


$n = 1, 2$
(XI-37)

also showed a typical morphine-like picture in the cat without evidence of convulsant action and almost without emetic effect.[28]

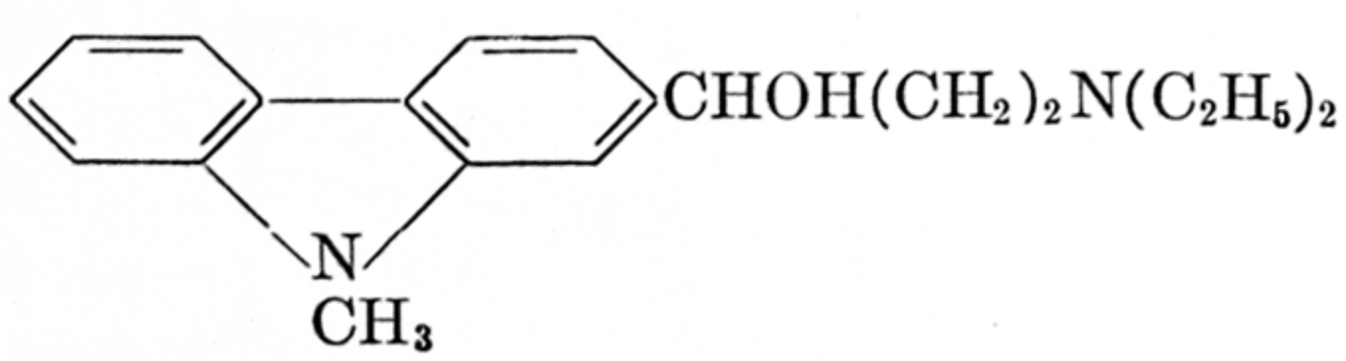
[28] Burger and Mosettig, *J. Am. Chem. Soc.*, **58,** 1570 (1936).

In the series of dibenzofuran compounds, a similar regularity as in the series of phenanthrene derivatives was observed. Particularly amino alcohols of the structure (XI-37) were more pronouncedly analgetic than in the phenanthrene series but this increase in beneficial activity was accompanied by an increase in toxicity. The same held also for derivatives of dibenzothiophene (XI-38). They had been suspected to be isosteres of the corresponding phenanthrene derivatives (XI-35), but the work of Burger and Bryant[29] has not supported physical evidence for this analogy.

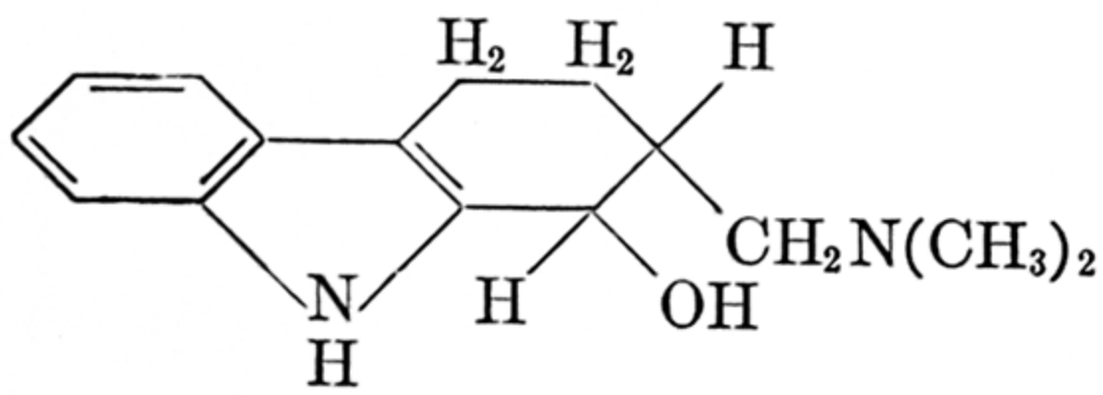


(XI-38)

In the carbazole series, the most active derivatives were 2-(3-diethylamino-1-hydroxy-*n*-propyl)-9-methylcarbazole (XI-39) and 1-hydroxy-2-(dimethylaminomethyl)-1,2,3,4-tetrahydrocarbazole (XI-40). They have



(XI-39)



(XI-40)

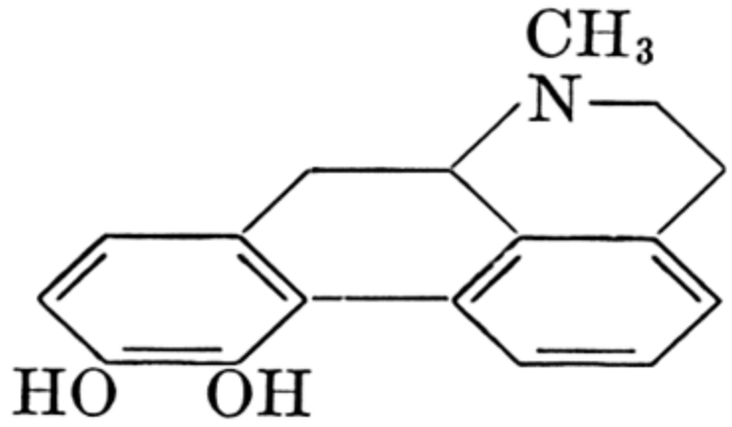
a smaller minimum effective dose, and a longer duration of analgetic action than any of the phenanthrene or dibenzofuran derivatives which have been studied. While these carbazole derivatives are also less toxic and less convulsant in cats, the most active substances are more emetic than the analogous derivatives of phenanthrene.

2. Apomorphine and Papaverine

In contrast to morphine, its rearrangement product apomorphine (XI-41) no longer has analgetic activity; it is a strong excitant for the

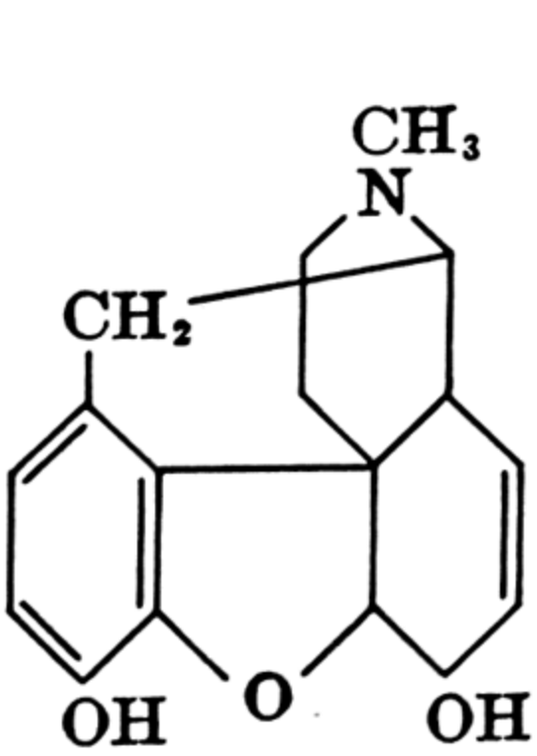
[29] Burger and Bryant, *J. Am. Chem. Soc.*, **63,** 1054 (1941).

central nervous system and, in small doses, may be used as an expectorant. Its chief use is as an emetic in cases of poisoning.

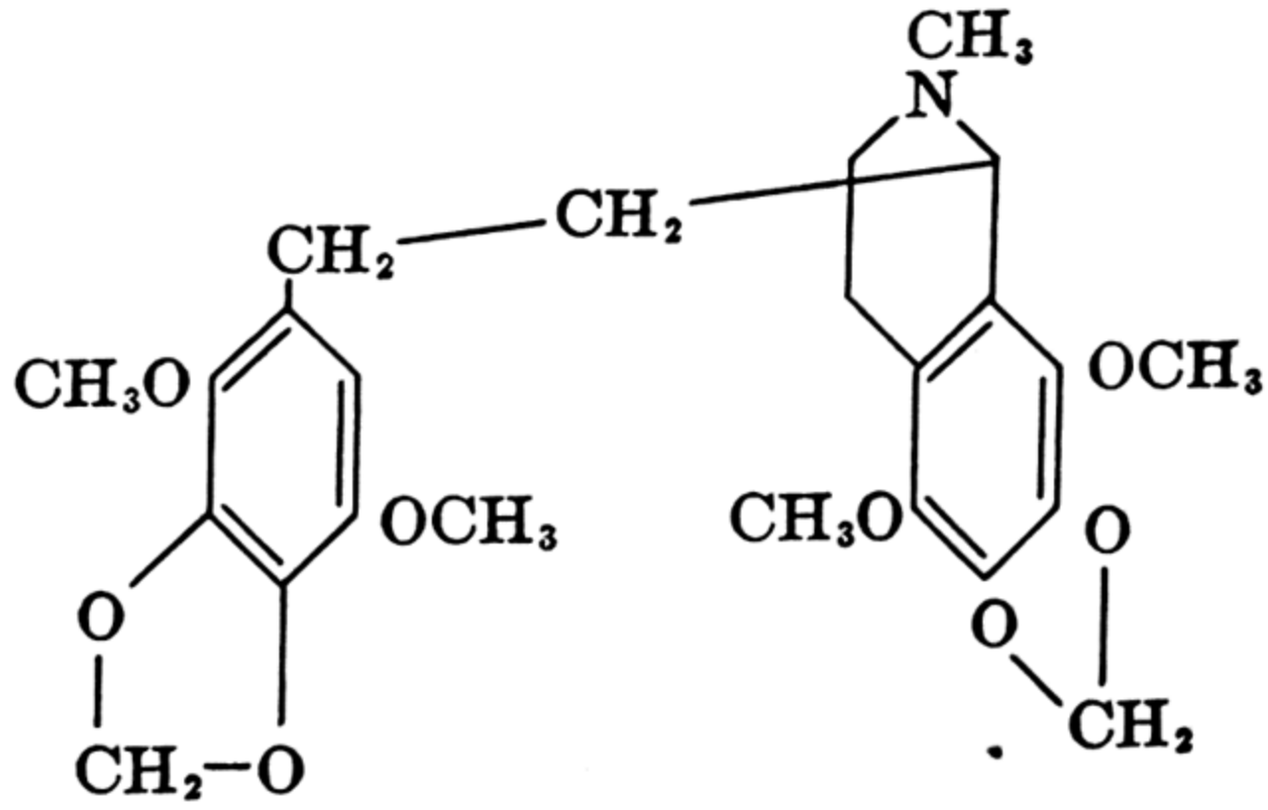


(XI-41)

The generic relation of morphine to its companion alkaloid papaverine and the mildly depressant and pronounced antispasmodic properties of the latter have instigated a number of studies concerning the analgetic potency of 1-aralkyltetrahydroisoquinoline derivatives. For instance, Külz[30] found that highly substituted derivatives of this kind (XI-42) led to substances possessing analgetic activity, and the intensity of this effect was stated to be approximately proportional to the number of substituents. A resemblance of these compounds to morphine may be expressed by comparison of their formulas.



(XI-1)

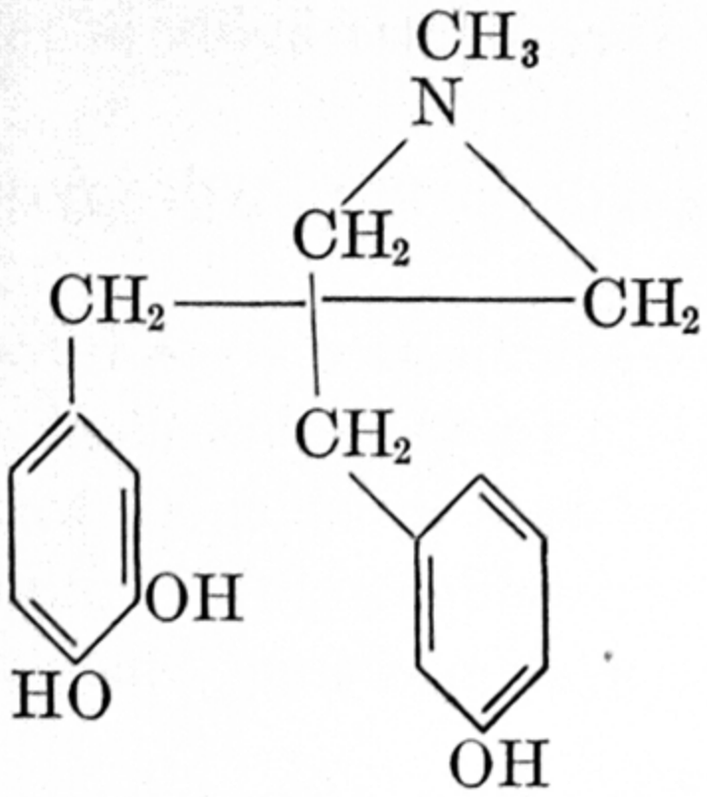


(XI-42)

3. The Ether Bridge

Although the opening of the ether bridge in morphine greatly decreases analgetic activity, and the opening of the piperidine ring in the morphimethines virtually abolishes this valuable property, several N-hydroxyphenylalkylene-dihydroxyphenylaliphatic amines of the general formula (XI-43 = XI-44) in which the alkyls contain from 4 to 10 carbon atoms have been tested.[31]

[30] Külz *et al.*, German Pat. Appl. K 150, 382, IV C/12p (1938).
[31] Külz *et al.*, U. S. Pats., 2,276,618; 2,276,619.



(XI-43)

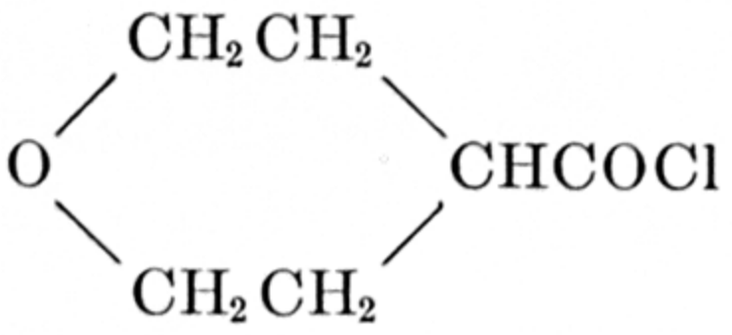
$$= (HO)_2C_6H_3(CH_2)_nNR(CH_2)_nC_6H_4OH$$

(n = 4 to 10)

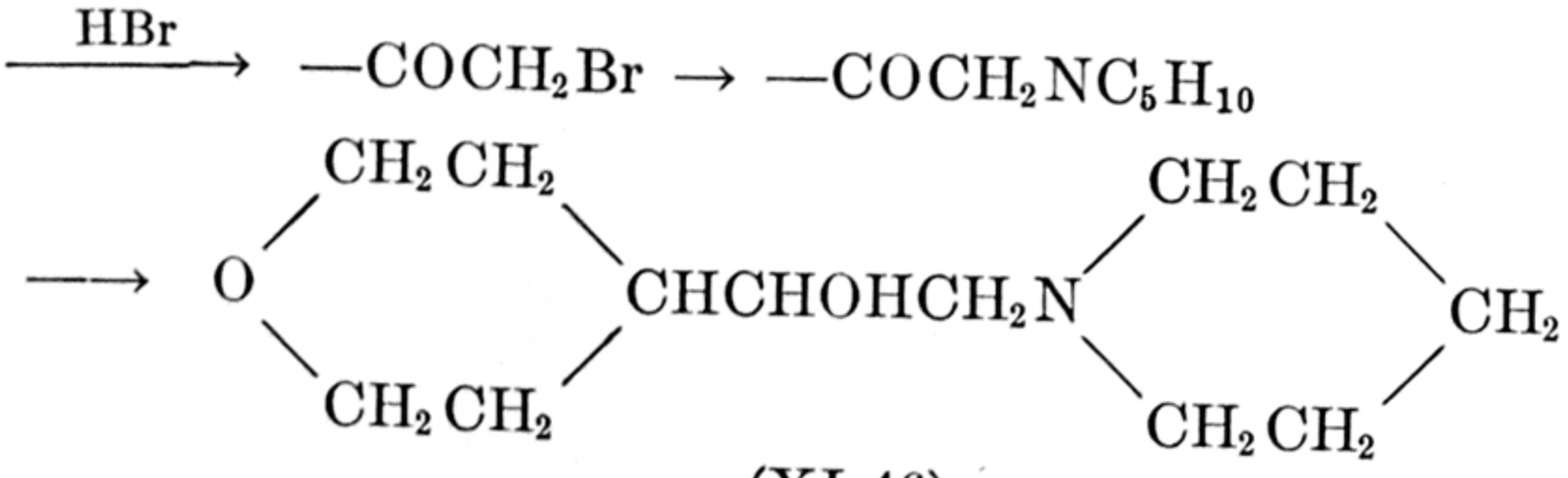
(XI-44)

The analgetic potency of these drugs is said to increase with the total number of the carbon atoms in the aliphatic chains connecting the nitrogen to the aromatic nuclei.

On the assumption that the oxygen bridge is necessary for analgetic activity in morphine, several tertiary furan amino alcohols were tested but were devoid of analgetic activity.[32] Based on similar considerations, Burger and his co-workers[33] prepared tetrahydropyranyl and tetrahydrofuryl amino alcohols. The pattern of the synthesis of these compounds is shown in the accompanying diagram. Tetrahydropyranoyl chloride (XI-45) was converted to the diazo ketone, the corresponding bromo ketone, and the corresponding amino ketones which were reduced to amino alcohols. The piperidino (XI-46) alcohol was the most active drug of the group,



(XI-45)



(XI-46)

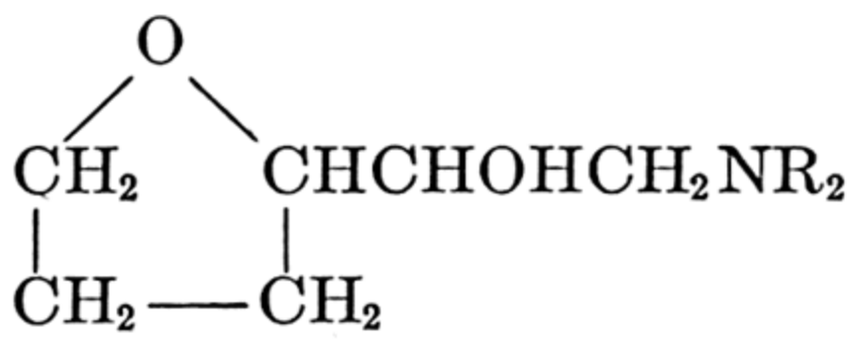
[32] Heneka, *Medicine in its Chemical Aspects*, Vol. III, Bayer, Leverkusen, 1938, p. 380.

[33] Harnest and Burger, *J. Am. Chem. Soc.*, **65,** 370 (1943). Burger, Bennet, Turnbull, and Dinwiddie, *Abstracts*, Meeting Am. Chem. Soc., Philadelphia, Pa., April 11, 1950, p. 13K.

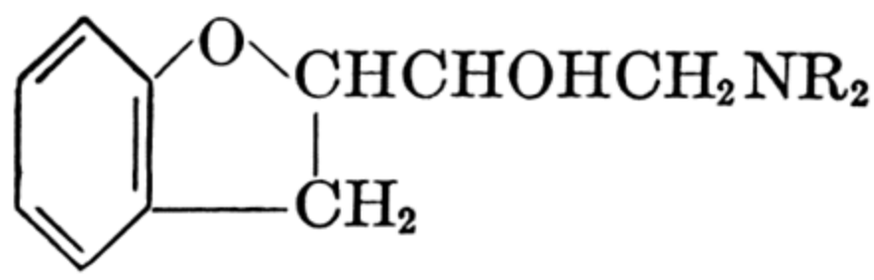
150 mg./kg. cat causing marked analgesia. Its therapeutic index in rats was 1:5.

Introduction of a phenyl group in the 4-position of the tetrahydropyran ring of such compounds abolished analgetic activity.[33]

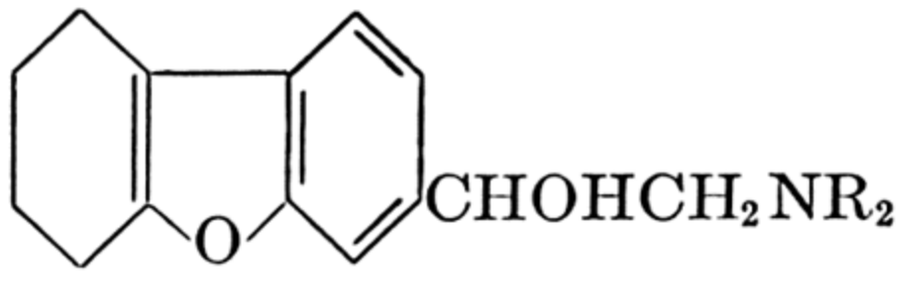
Tetrahydrofuryl amino alcohols (XI-47) were synthesized from furoyl chloride in an analogous manner, the intermediate furyl amino alcohols being hydrogenated as the final operation. They were much more toxic than the tetrahydropyranyl analogs. Similar benzodihydrofuryl amino alcohols[34] (XI-48) in which the benzodihydrofuran system of morphine was



(XI-47)



(XI-48)



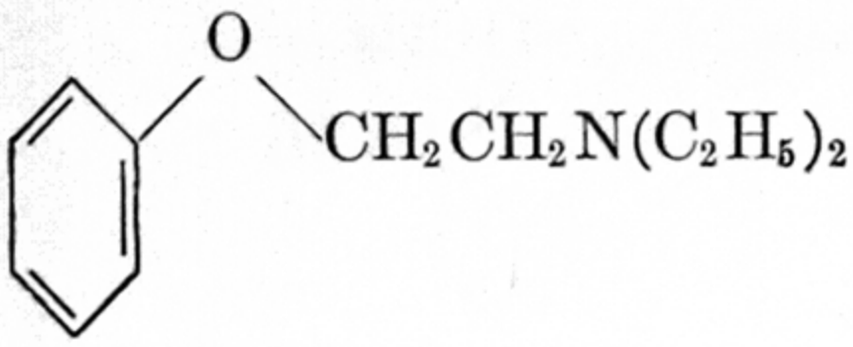
(XI-49)

to be simulated shared this property. Amino alcohols derived from dibenzofuran[35] carrying the functional groups in the side chain or in a partly hydrogenated ring (XI-49) were much more active, but also more toxic than the corresponding derivatives of phenanthrene.

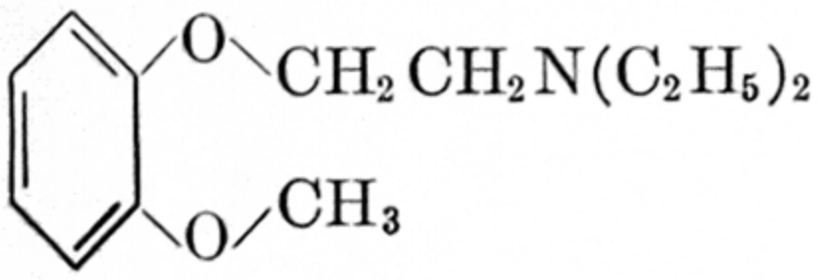
The significance of the furan-type ether bridge for the analgetic activity of morphine is now seriously open to question, since the synthetic N-methylmorphinans (XI-79, 89) which lack this group, exhibit very high analgetic properties.

In the group of cyclic ethers containing basic functions, the earliest compounds recognized to exhibit an antihistaminic effect were also found to have analgetic properties. These compounds were studied originally for their inhibition of nervous impulses in the sympathetic system. Their sedative action, observed in doses of 20–30 mg./kg. seems to be independent of their antiadrenergic properties. They are listed here in the order of decreasing activity.[36]

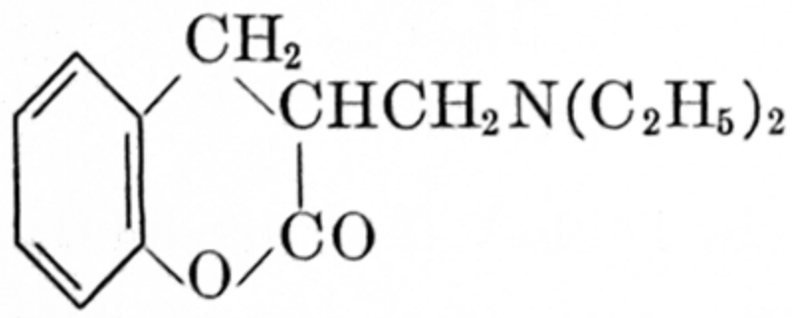
[34] Burger and Deinet, *J. Am. Chem. Soc.*, **67,** 566 (1945).
[35] Mosettig and Robinson, *J. Am. Chem. Soc.*, **57,** 2186 (1935).
[36] Bovet and Bovet-Nitti, *Médicaments du Système Végetatif*, Karger, Basel, 1948, p. 247; Interscience, New York.



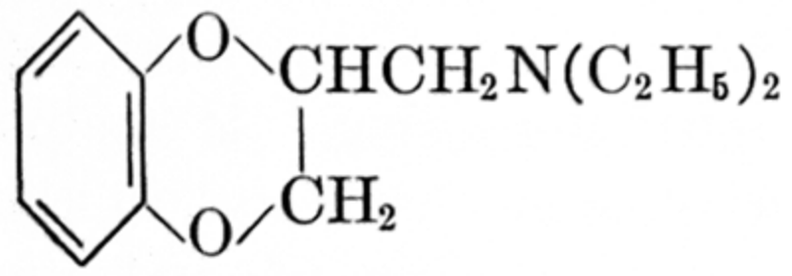
$CH_2CH_2N(C_2H_5)_2$ — β-Diethylaminoethoxybenzene



$CH_2CH_2N(C_2H_5)_2$ — *o*-Methoxy-β-diethylaminoethoxybenzene



$CHCH_2N(C_2H_5)_2$ — 3-Diethylaminomethylcoumarin



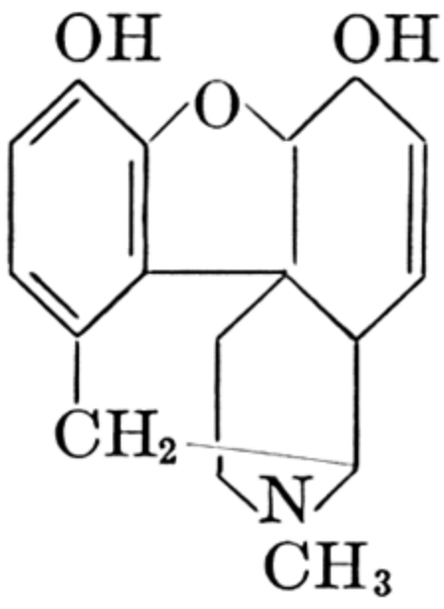
$CHCH_2N(C_2H_5)_2$ — 2-Diethylaminomethylbenzodioxane

4. Demerol

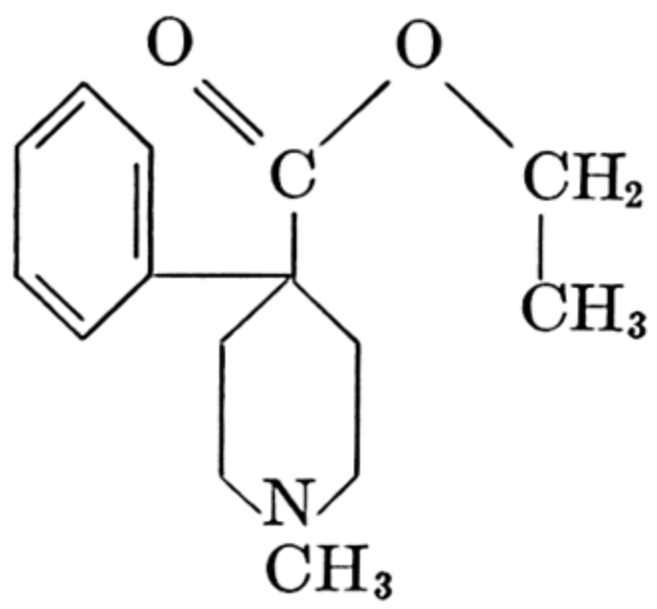
In 1937, Eisleb and Schaumann[37] prepared a number of simple piperidine derivatives with the avowed purpose of testing them as antispasmodics because of a rather vague structural similarity to atropine. During the tests it became apparent that some of these compounds were endowed with potent analgetic activity. A *post-facto* inspection of their molecular structure (XI-50) revealed certain similarities to the formula of morphine (XI-1). If this alkaloid is regarded as a derivative of phenethylamine, and its euphoric action is attributed to that structural feature which is also present in such pronounced euphorics as mescaline (XI-51), then a severing of the phenethylamine chain, that is a break between the nitrogen atom and the aromatic ring, should perhaps produce compounds with less euphoric action. In Demerol[38] (Meperidine, XI-50), this prediction has been largely realized.

The two syntheses used by Eisleb in the preparation of the Demerol series permitted a sufficient variation of the structures without profoundly changing the synthetic approach. Approximately forty piperidine derivatives containing in the 4-position an aromatic ring and a number of unsaturated functions, such as keto, nitrile or ester groups were tested, and of these the combination with the most favorable therapeutic index was chosen

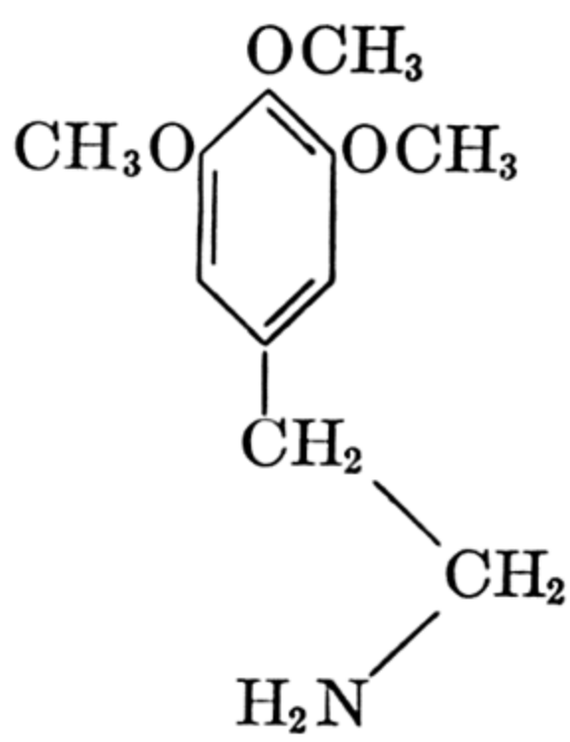
[37] Eisleb and Schaumann, *Deut. med. Wochschr.*, **1939,** 967.
[38] Other names: Meperidine, Pethidine, Isonipecaine, Dolantin.



(XI-1)



(XI-50)



(XI-51)

for clinical trial. As may be seen from the data in Table V the introduction of hydroxyl, methoxyl, or amino groups in the para position of the aromatic ring decreases or abolishes analgetic effects. Analgetic action also disappears if the benzene ring is replaced by a naphthalene ring. It should be noted, however, that the introduction of a phenolic hydroxyl in the meta-position in the aromatic ring causes a five-fold increase of analgetic activity. It has been suggested that this molecule is more comparable in structure to morphine than Demerol.

Removal of the methyl group from the nitrogen, or replacement of this methyl group by other groups generally decreases or abolishes analgetic properties. No other group in place of the carbomethoxy group in Demerol, such as other ester groups, ketone, amide or carbinol groups, with the exception of the propyl ketone group show the same high analgetic effect. All these compounds are distinguished by a high degree of antispasmodic activity which is usually more pronounced than their analgetic function. They are relatively devoid of euphoric action.

Only one such analog of Demerol, 4-(*m*-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone (XI-54), also called Ketobemidone, shows highly increased activity. It is thirty times more effective than Demerol, but unfortunately leads rapidly to very severe addiction so that its clinical use has been judged inadvisable.[39a]

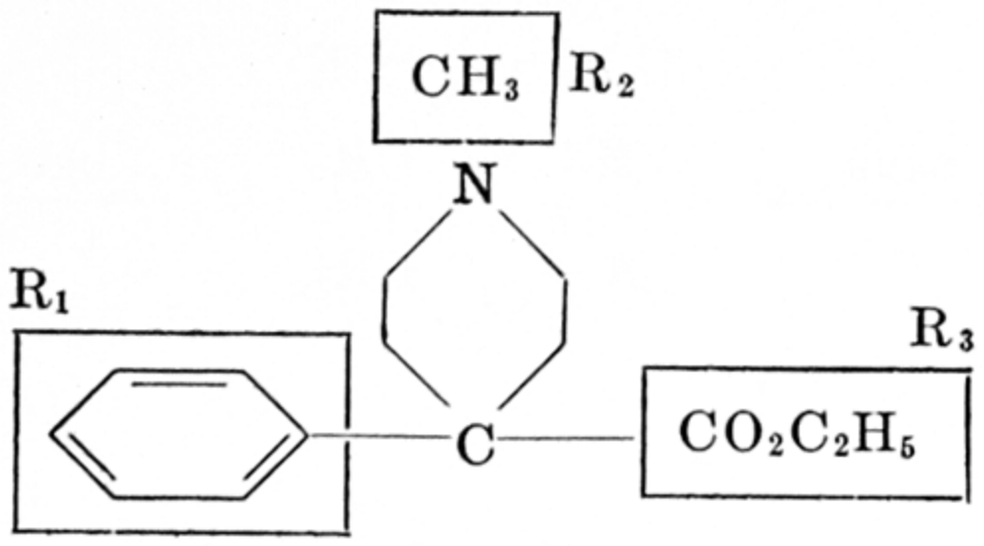
An interesting modification of the Demerol structure has been presented in 4-(6-hydroxy-3-methylphenyl)-1-isonipecotic acid lactone (XI-54a) in which the carboxyl is esterified with an *ortho*-phenolic hydroxyl group in the benzene ring. The compound shows considerable analgetic activity in man.[39b]

Demerol has found wide clinical acceptance and has been able to replace morphine in a number of conditions requiring powerful analgesia

[39a] cf. Eddy, *J. Am. Pharm. Assoc.*, **39,** 245 (1950). Kägi and Miescher, *Helv. Chim. Acta*, **32,** 2489 (1949). Bernstein, *Schweiz. Med. Wochschr.*, **79,** 1159 (1949).

[39b] Spielman, U. S. Pat. 2,500,714 (1950).

TABLE V. PHARMACODYNAMIC ACTIVITY OF ANALOGS OF DEMEROL[37]



	Analgesia	Antispasmodic Activity against spasms induced by		
		Choline Carbamate	$BaCl_2$	Histamine
Demerol (XI-50)	1	1	1	1
R_1 = *p*-hydroxyphenyl	0.2	0.25	0.75	0.2
p-methoxyphenyl	0	0.25	1	0.2
p-aminophenyl	0.16	0.25	0.33	0.33
α-naphthyl	0	0.33	3	2
R_2 = H	0.15	1	0.5	0.75
C_2H_5	0.75–1.0	1	1	0.75
n-C_3H_7	0.5	0.16	0.25	0.25
n-C_4H_9	0.75–1.0	0.14	1	0.33
CH_2CH_2OH	0.25	0.25	1	0.33
R_3 = $COOCH_3$	0.75–1.0	1	0.5	1
$COOC_4H_9$	0.16	1	1.5	1.5
$COOC_6H_5$	0.2	1	2	1
COC_2H_5	0.5	1	1	0.33
$COCH(CH_3)_2$	0.5	2	2	0.16
$COCH_2CH_2CH_3$	1	1	1	0.5
$COCH_2CH(CH_3)_2$	0.5	3	1.5	1
COC_6H_{11}(cycl.)	0.25	3	3	0.33
$COCH_2CH_2C_6H_5$	0.25	1	5	0.1
CO-*p*-C_6H_4OH	0.25	4	1	1
CO-*p*-$C_6H_4OCH_3$	0.5	1	3	0.1
R_2 = cyclohexyl				
R_3 = $COCH_2CH_3$	0.5	0.25	1	0.1
R_2 = $CH_2C_6H_5$				
R_3 = $COCH_2CH_3$	0.5	0.04	2	0.03

particularly in preoperative and post-surgical practice. Withdrawal symptoms and mild euphoria have been observed occasionally, but they are milder and more easily overcome than those caused by morphine.)

The analog of Demerol called β-pethidine (XI-52) in which the 3- instead of the 4-position of the piperidine ring is substituted possesses less sedative qualities and may thereby segregate these overlapping effects more

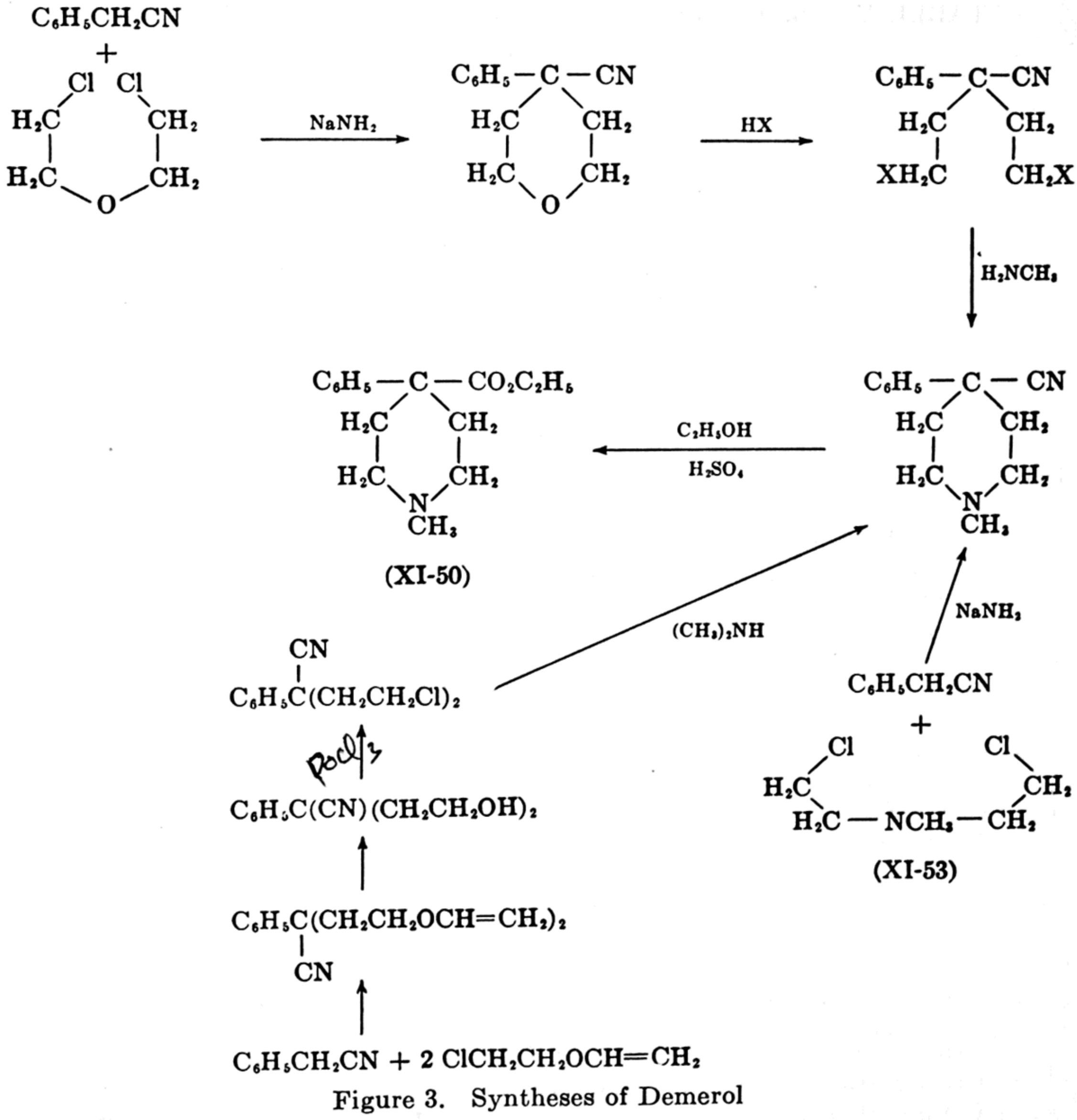
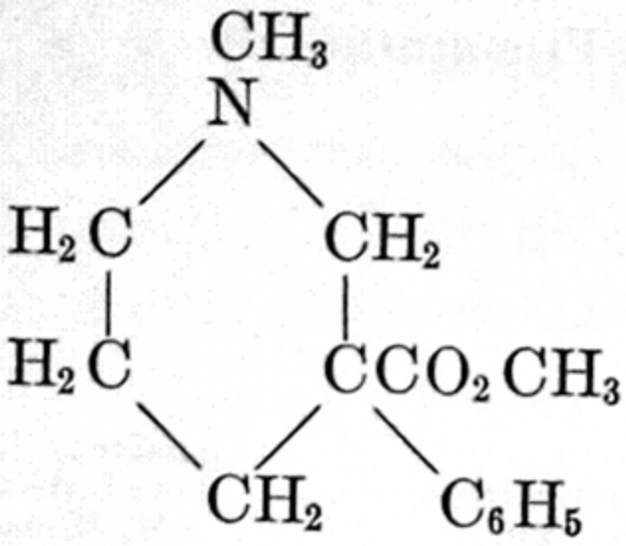


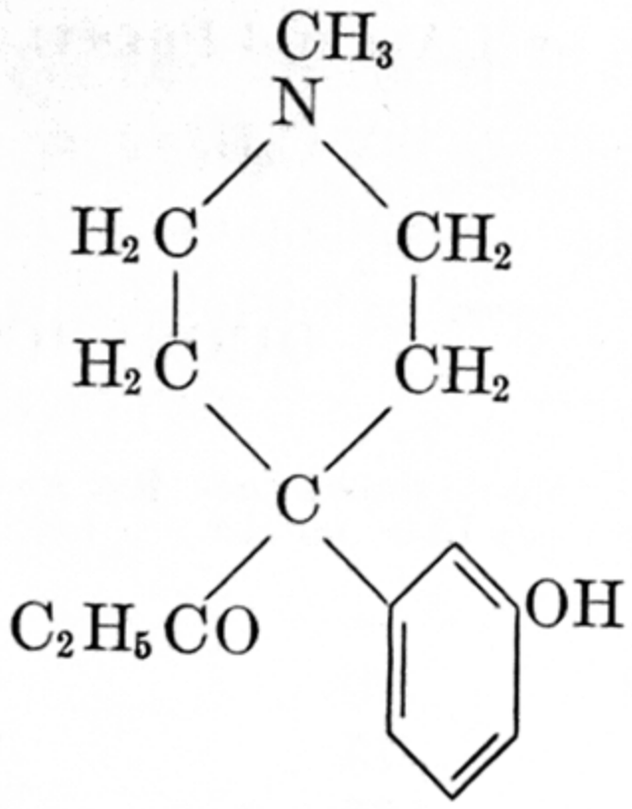
Figure 3. Syntheses of Demerol

effectively than Demerol itself.[39]

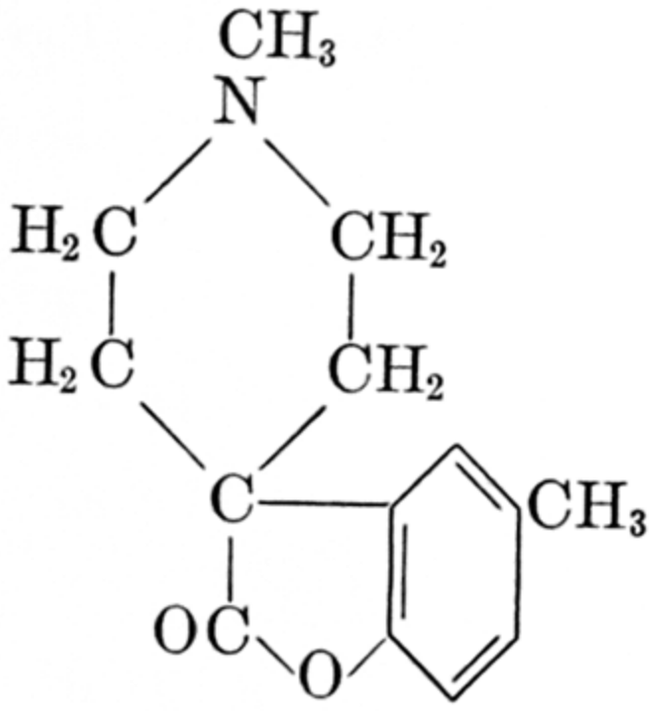
For the synthesis of Demerol, Eisleb[40] first condensed benzyl cyanide with β,β-dichloroethyl ether, and replaced the pyran oxygen by the methylamino group by a series of operations shown in Figure 3. Later, bis-(β-chloroethyl) methylamine (XI-53) was used in the condensation, and the route to Demerol was substantially shortened. The convenience of this route is marred by the fact that bis-(β-chloroethyl) methylamine is a powerful vesicant. In an effort to synthesize the drug by a less trying route from a practical point of view, Bergel and coworkers[41] condensed phenylacetonitrile with β-chloroethyl vinyl ether and hydrolyzed the resulting compound to a diol which on chlorination and condensation with methylamine gave the nitrile from which Demerol had already been obtained by alcoholysis.



(XI-52)



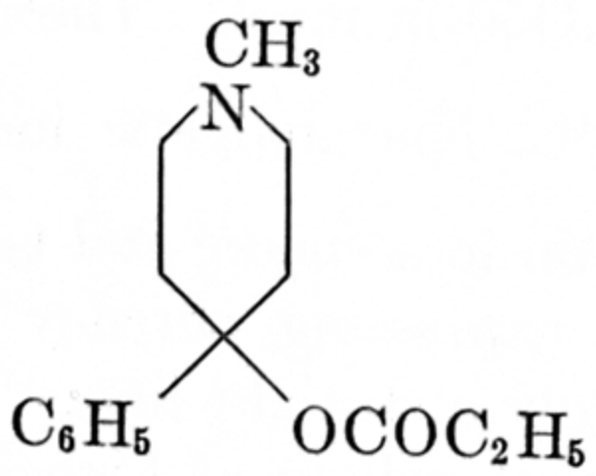
(XI-54)



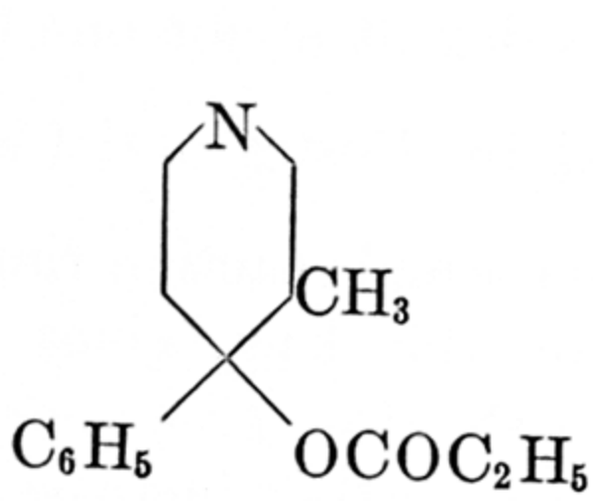
(XI-54a)

5. Derivatives of 4-Piperidinol

If the carbomethoxy group in Demerol is regarded as a partial carrier of the functions of rings III and V of the morphine molecule, it becomes apparent that it is the shape of the whole Demerol molecule which is important in comparison with that of morphine rather than the exact replica of any section of the latter molecule. It is not surprising to find that such a compound as 4-phenyl-4-hydroxy-1-methylpiperidine propionate (XI-55), a derivative of 4-piperidinol in which the ester group has been reversed, has about $\frac{1}{7}$ the analgetic activity of morphine.[42] Introduction of a



(XI-55)



(XI-56)

methyl group into position-3 of the piperidine ring increases the analgetic effect of (XI-55) to 5.5 times that of morphine.[43] The resulting drug, 1,3-dimethyl-4-phenyl-4-propionoxypiperidine (XI-56, Nisentil) has been reported useful in relieving acute pain as it is encountered in obstetrics.

Variations of the alkyl groups in (XI-55) have led to a long series of compounds a few of which are tabulated below. In Table VI are listed,

[39] McDonald, Woolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, **1,** 4 (1946). Bergel, Hindley, Morrison, and Rinderknecht, *J. Chem. Soc.*, **1944,** 269.

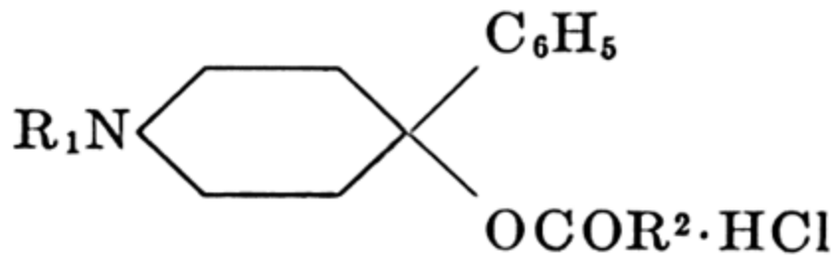
[40] Eisleb, *Ber.*, **74,** 1433 (1941).

[41] Bergel, Morrison, and Rinderknecht, *J. Chem. Soc.*, **1944,** 265.

[42] Lee, Ziering, Berger, and Heineman, in *Jubilee Volume Emil Barell,* Reinhardt, Basle, 1946, p. 267–9; *J. Org. Chem.*, **12,** 885, 894 (1947). Berger, Ziering, and Lee, *ibid.*, **12,** 904 (1947).

[43] Ziering and Lee, *J. Org. Chem.*, **12,** 911 (1947).

TABLE VI. ESTERS OF 1-ALKYL-4-PHENYL-4-PIPERIDINOLS[44]



R_1	R_2	Mouse Subcutaneous LD_{50}, mg./kg.	Rat Analgetic Dose 1.40; mg./kg.	Analgetic Index at about 1/3; Mouse LD_{50}
CH_3	C_2H_5	40	1.4	1.55
CH_3	C_3H_7	75	8.5	1.58
C_2H_5	C_2H_5	75	2.2	1.55
C_2H_5	C_3H_7	70	12	1.58
C_4H_9	C_3H_7	145	10	1.60
C_4H_9	C_2H_5	115	3.5	1.57
CH_3	CH_3	300	40	1.55
C_4H_9	CH_3	170	21	1.56
Allyl	C_2H_5	110	4.5	1.42
$CH(CH_3)_2$	C_2H_5	65	2.3	1.48
C_3H_7	C_2H_5	85	5.3	1.36
Demerol		196	43.6	1.50
Morphine Sulfate		360	3.75	1.60

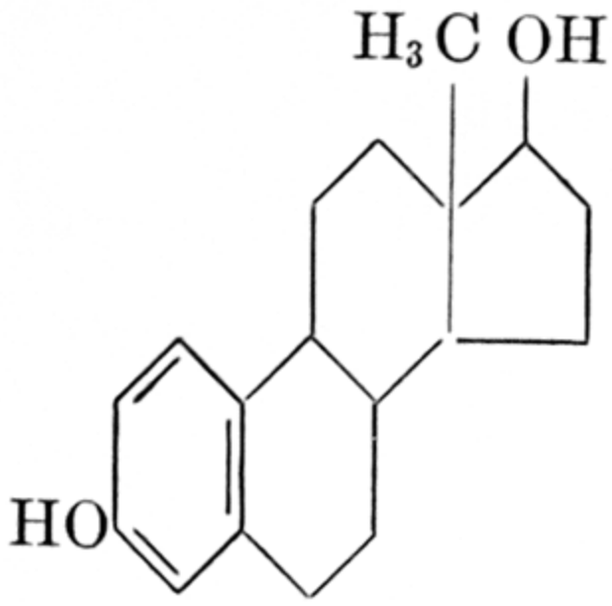
after the subcutaneous LD50 in mice, the analgetic dose 1.40 in rats, and the analgetic index at about one third LD50 in mice. These terms have been explained by Foster and Carman.[44] The analgetic index $\sqrt{\frac{t_2}{t_1}}$, in which t_1 is the normal reaction time to pain in seconds, and t_2 the reaction time altered by the drug, gives figures expressing potency which when plotted against the dose give approximately a straight line. Because rats do not show any further increase of pain threshold at higher figures, the analgetic index of 1.40 was chosen as a reference for complete analgesia; it represents about twice the normal reaction time. The dose giving this index is termed the rat analgetic dose 1.40.

6. The Experiments of Dodds

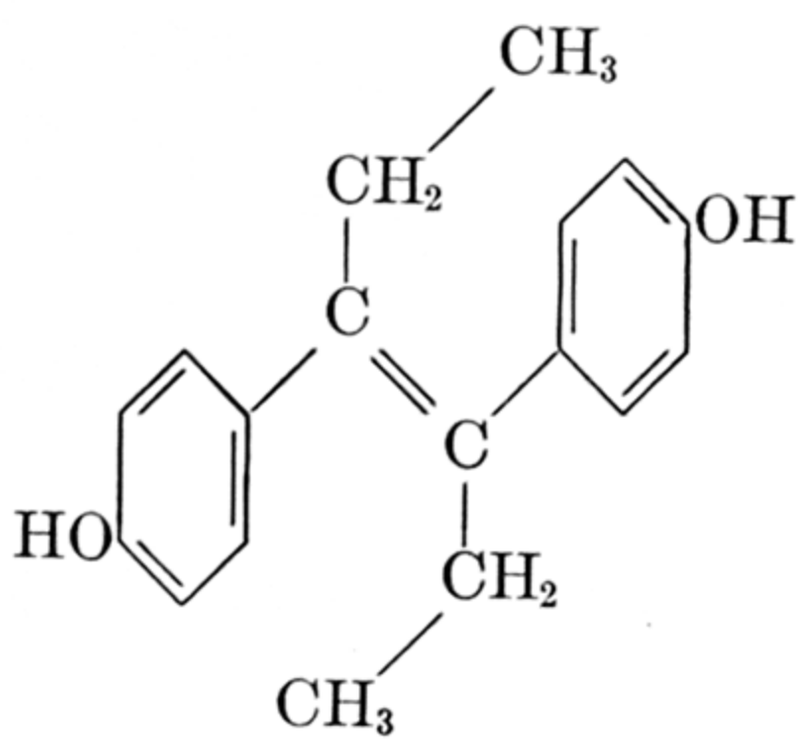
The desire to simulate the peculiar sterical set-up of morphine motivated also the experiments of Dodds.[45] They were based on an experience with stilbestrol (XI-58) which had been designed successfully as an "open-chain" female sex hormone (XI-57) (Chapter XXIX). Since morphine also contains a phenanthrene ring system, it appeared possible to open

[44] Foster and Carman, *J. Pharmacol. Exptl. Therap.*, **91,** 195 (1947).
[45] Dodds, Lawson, and Williams, *Proc. Roy. Soc.*, **B132,** 119 (1944); *J. Physiol.*, **104,** 47 (1945).

similarly some of its rings, and therefore a series of diphenylethylamine derivatives was tested. Actually 200–400 miligrams of β-phenylphenethylamine (XI-59) given in four hourly doses was able to replace morphine, but it only relieved the pain associated with pressure on nerves caused by

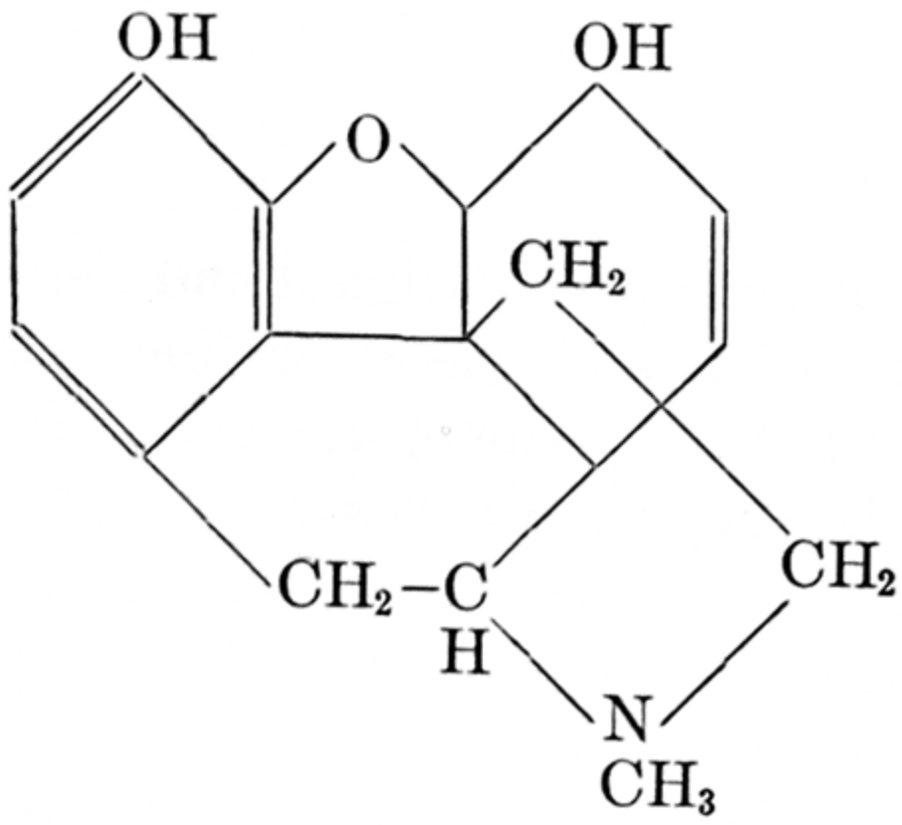


(XI-57)

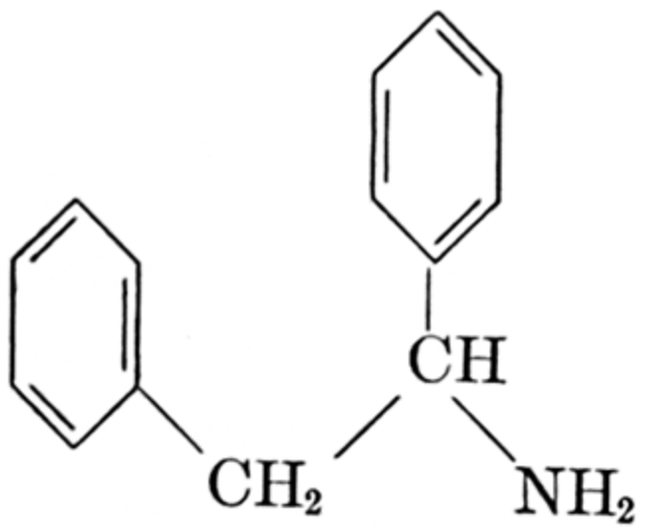


(XI-58)

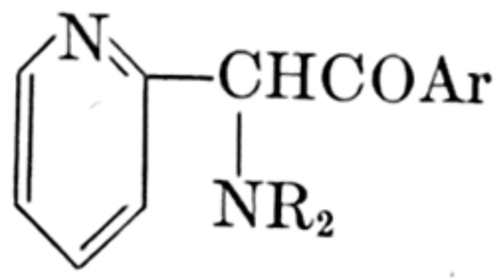
malignant growth and had no effect on other types of pain. When a rise in the pain threshold was measured by the electric stimulus method this compound was found to be devoid of analgetic action. On the other hand, several phenacylpyridine derivatives (XI-60) cause marked analgesia in animals.[46]



(XI-1)



(XI-59)



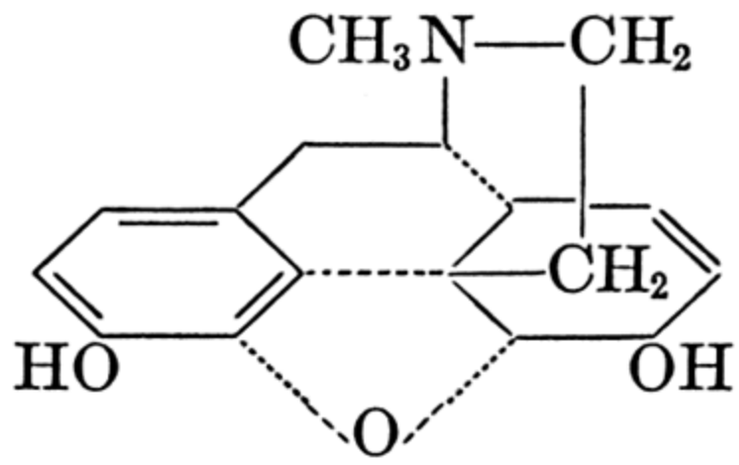
(XI-60)

7. Lee's Studies

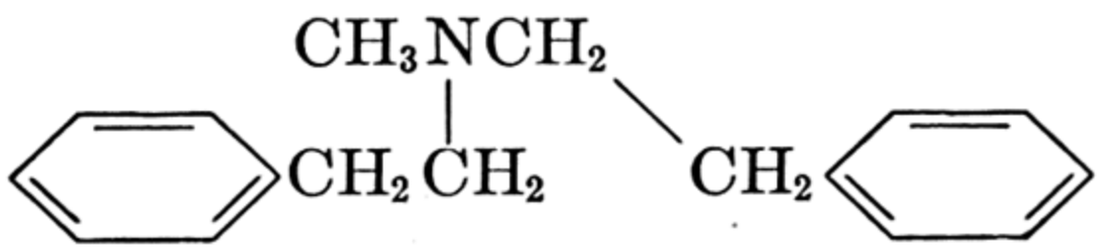
Apart from the 4-phenylpiperidine structure encountered in Demerol a number of other partial structures can be "extracted" from the skeleton of morphine, which if modified could be expected to produce analgetic compounds. In emphasizing the connecting link between the terminal nuclei of the phenanthrene portion of morphine by way of the nitrogen

[46] Smith, U. S. Pat. 2,442,865 (1948).

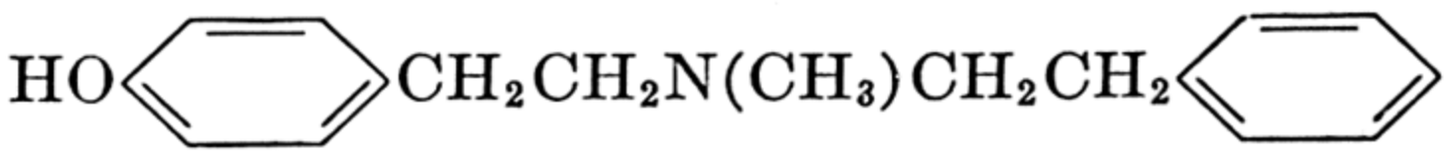
atom, Lee and coworkers[47] arrived at tertiary bis (phenethyl) amines (XI-61). The *p*-hydroxy derivative (XI-62) which shows the closest structural



(XI-1)



(XI-61)



(XI-62)

resemblance to the opiate prototype, had the highest analgetic activity of this series, about $\frac{1}{7}$ that of morphine. These compounds are similar to those described by Külz[31] and also resemble the antispasmodics of the Sestrone type (Chapter XXIII).

8. Methadon

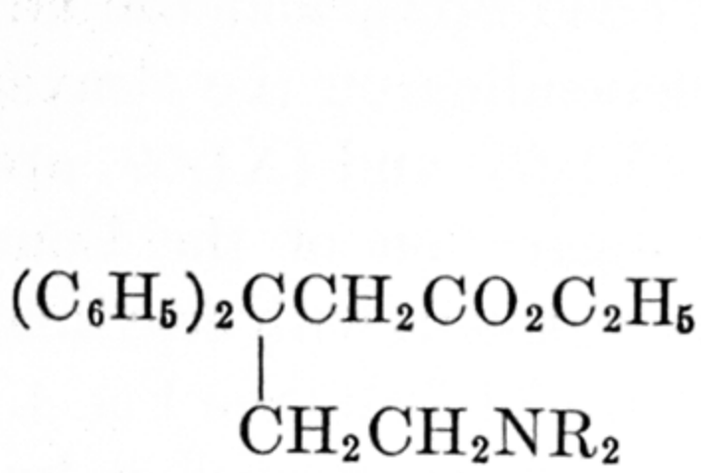
The most outstanding structural feature shared by Demerol and morphine is the quaternary carbon atom in position-4 of the piperidine ring which throws in morphine one of the rings out of the plane of the remaining system and which assembles both molecules in a rigid sterical pattern. The only previously described piperidine derivative which had an approximately similar arrangement at carbon-4 was α-Eucaine (Merlin, 1896). It had a local anesthetic action like cocaine (Chapter VIII).

A re-design of the fragments of the morphine molecule which point to the importance of carbon-4 of the piperidine system may have been at the bottom of the approach of Bockmühl and Schaumann during the past war which culminated in the synthesis of methadon, one of the most potent useful synthetic analgetics. This drug, also named Amidone, Dolophine or Adanon, bears a great resemblance to the ethyl β-(β-dialkylaminoethyl)-β,β-diphenylpropionates (XI-63) which Bockmühl and Ehrhart[48] had

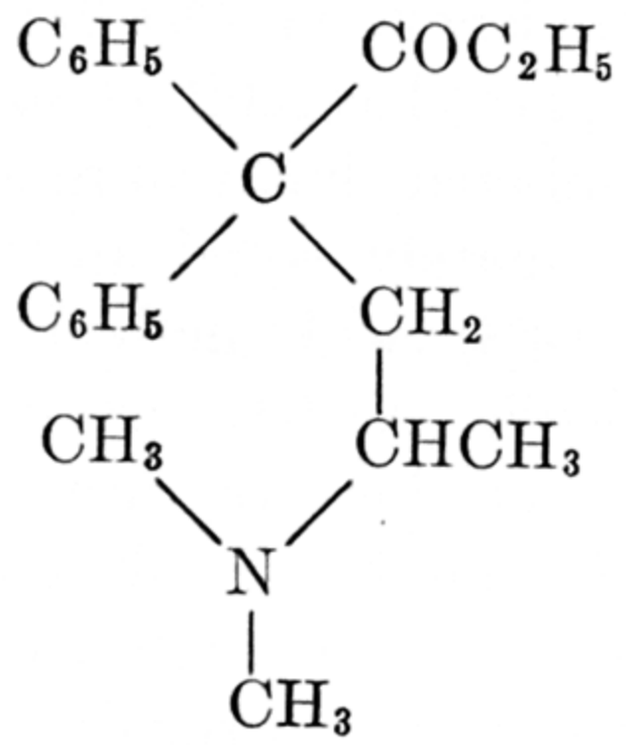
[47] Lee, Ziering, Berger, and Heineman, in *Jubilee Volume Emil Barell.* Reinhardt, Basle, 1946, p. 266, 270.

[48] Bockmühl and Ehrhart, Germ. Pat. 711,069.

described previously as spasmolytics and analgetics. Methadon (XI-64) may also have been an outcome of variations of the Demerol molecule with the piperidine ring opened.



(XI-63)



(XI-64)

Evidence has recently been furnished that methadon acts by interfering with the glycolytic enzyme, hexokinase, and thereby interrupts the normal carbohydrate energy supply to the central nervous system.[49] The synthesis

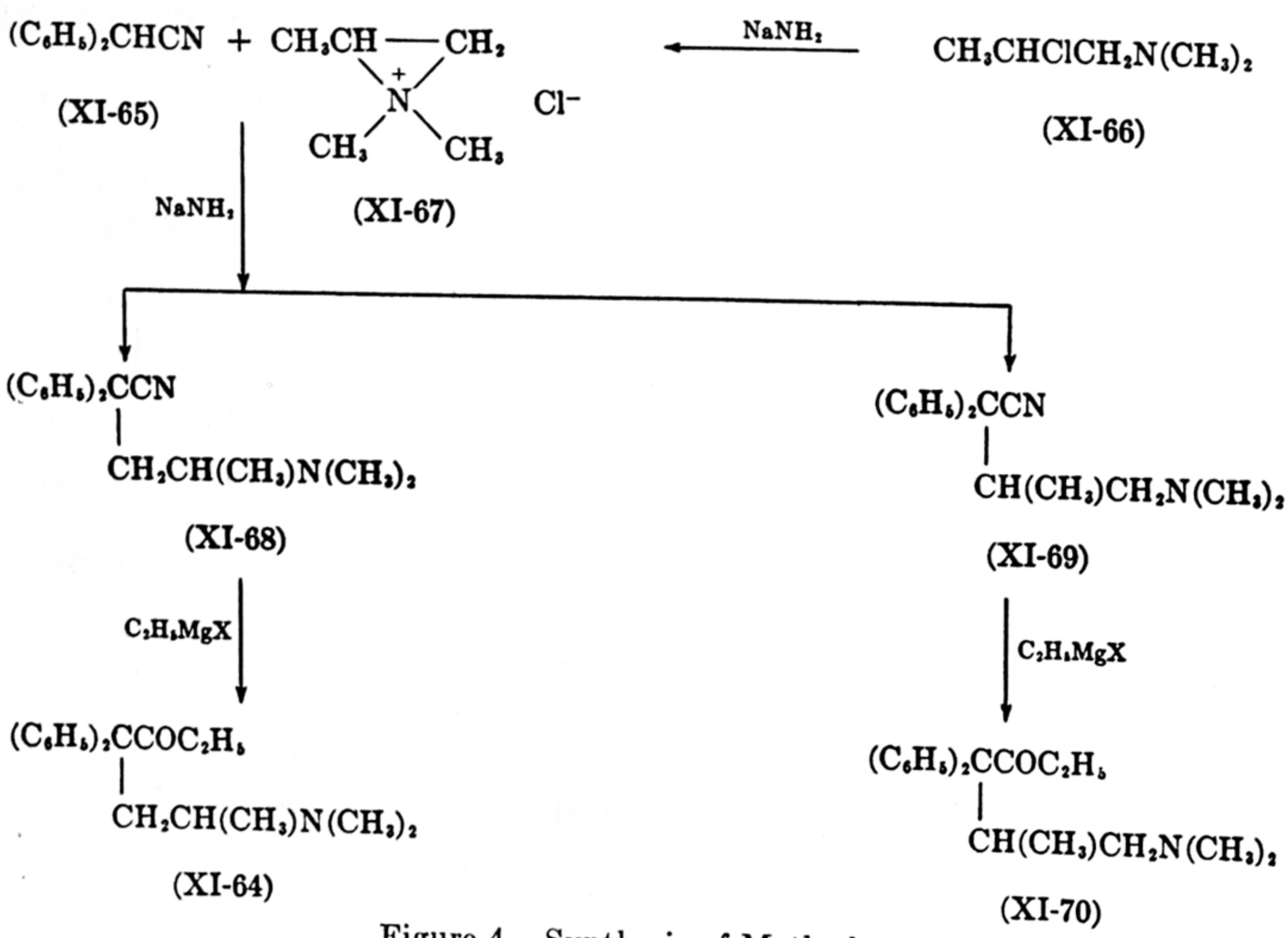
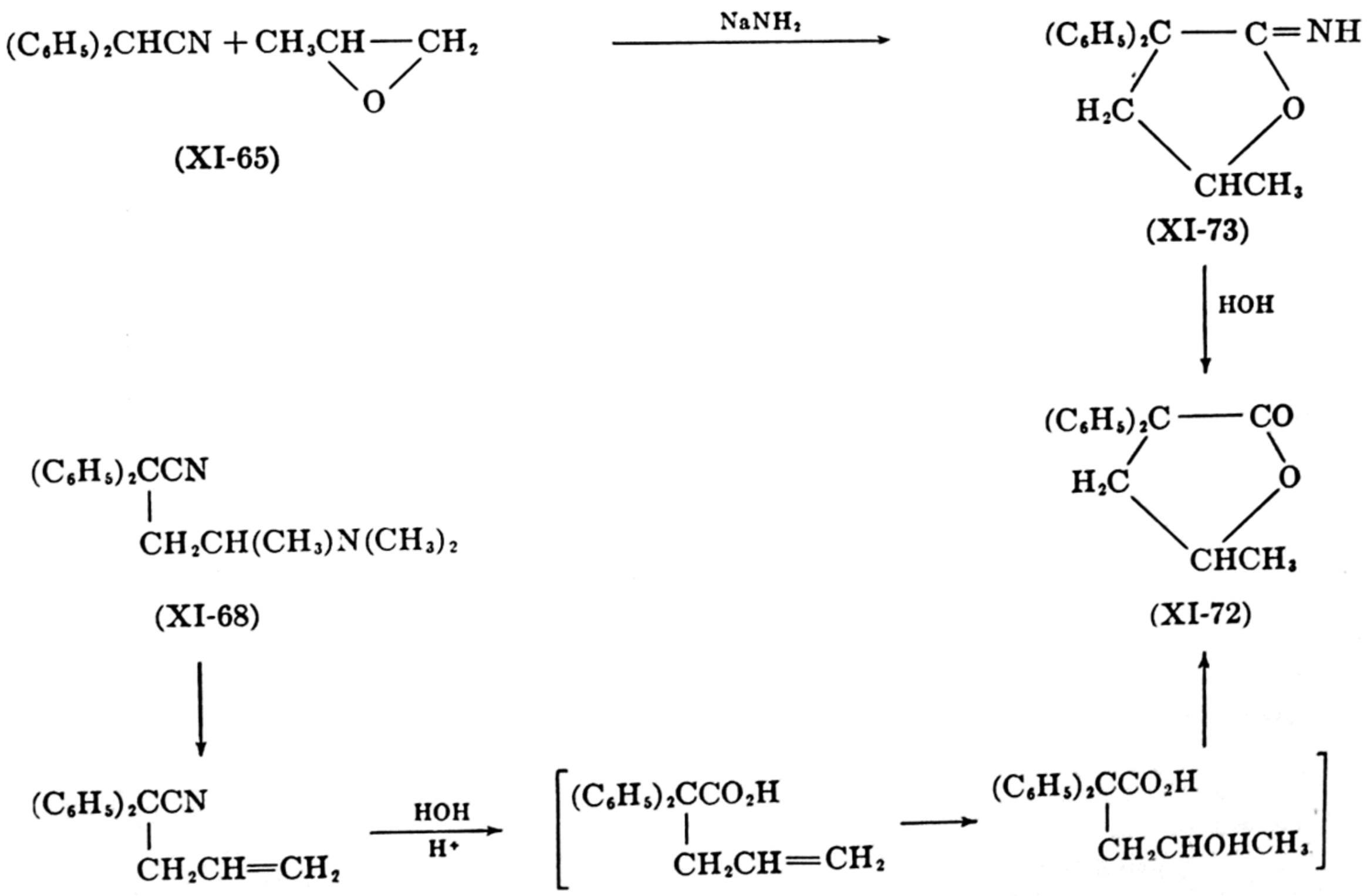


Figure 4. Synthesis of Methadon

[49] Greig, *Arch. Biochem.*, **17,** 129 (1948).

of methadon takes its start from diphenylacetonitrile (XI-65) which is condensed with 2-chlorodimethylaminopropane (XI-66) under the influence of sodamide. Since this chloroamine undergoes an intermediate cyclization to the ethyleneimine (XI-67) under these conditions, and the latter may add to diphenylacetonitrile in two ways, depending on the cleavage of its three-membered ring, two isomeric nitriles (XI-68) and (XI-69) are formed in approximately equal amounts. After separation of the isomers, the nitrile (XI-68) yields methadon (XI-64) on treatment with ethylmagnesium halides, while (XI-69) furnishes isomethadon (XI-70). (See Fig. 4.)

Proof of the structure of methadon has been furnished by several degradative methods, only one of which is presented here.[50] Exhaustive methylation of 4-dimethylamino-2,2-diphenylvaleronitrile (XI-68) leads to the unsaturated nitrile (XI-71) which can be hydrolyzed to 2,2-diphenyl-4-hydroxyvalerolactone (XI-72). The same lactone is also obtained from 3,3-diphenyl-5-methyltetrahydro-3-furanoneimine (XI-73) which can be prepared from diphenylacetonitrile (XI-65) and propylene oxide in the presence of sodamide.



(XI-65) (XI-73) (XI-72) (XI-68) (XI-71)

[50] Easton, Gardner, and Stevens, *J. Am. Chem. Soc.*, **69,** 2941 (1947); see for further references.

The imine (XI-73) also provides a starting material for an alternative synthesis[50] of the precursor nitrile of methadon. Treatment with phosphorus trihalide converts it to 4-halogeno-2,2-diphenylvaleronitrile (XI-74) which can be converted to (XI-68) with dimethylamine.

(XI-73) (XI-74)

$\xrightarrow{(CH_3)_2NH}$ (XI-68)

The optical resolution of methadon with tartaric acid has been accomplished.[51] The levo isomer is 2.2 times as active as morphine while the dextro-isomer shows only one tenth the activity of the alkaloid. However, the overall pharmacological behavior of the levo isomer is so similar to that of the racemic mixture that it would offer no advantage except the minor one of halving the small doses of the unresolved material.

The effective dose of methadon in man has been stated to be between two-thirds and three times that of morphine. It reproduces virtually every detail of morphine action including, to some extent, its addiction liability. There are indications that it can be substituted for morphine in addicts, and subsequent withdrawal from methadon is much less trying than that from morphine.[52]

Experiments with methadon containing C^{14}-labeled carbon have shown[52a] that the drug distributes itself fairly evenly throughout the animal, and no higher concentrations were found in the brain than in most of the body. Higher methadon levels accumulated in the adrenals, thyroid, lungs, spleen, kidney, liver and gastro-intestinal tract.

Of the structural isomers of methadon with a different arrangement in the basic side chain, only isomethadon (XI-70) is almost as strongly analgetic. It also exhibits fewer side reactions than methadon. Its *l*-isomer produces less nausea than morphine, *dl*-methadon and *dl*-isomethadon.

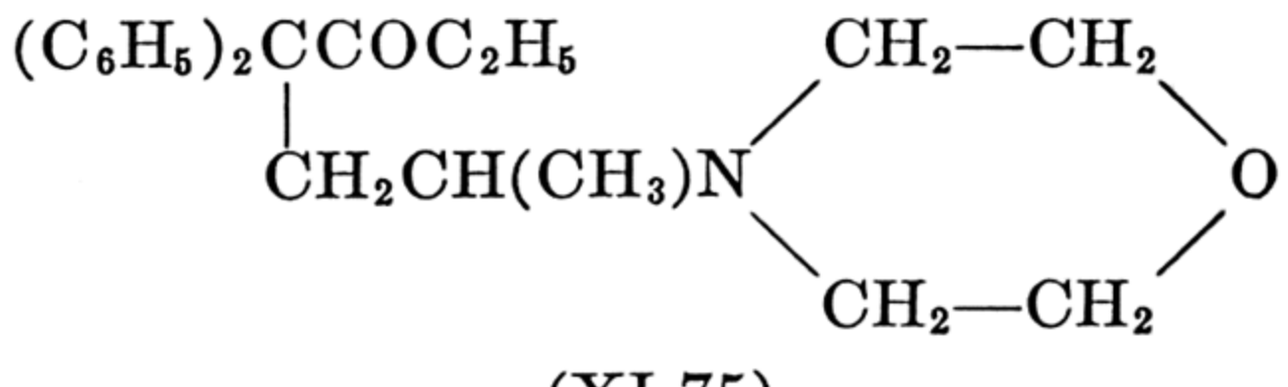
Changes in the ethyl ketone group of methadon are accompanied by characteristic pharmacological changes which parallel those in morphine when the alcoholic hydroxyl group of this alkaloid is acetylated, or oxidized to a keto group. The therapeutic index of methadon (2 to 3) rises to 40

[51] Thorpe, Walton, and Ofner, *Nature*, **160,** 605 (1947). Brode and Hill, *J. Org. Chem.*, **13,** 191 (1948).

[52] Eddy, "Progress in Drug Therapy of Pain," Memorial Vol. Am. Assn. of Pharmaceut. Manuf., New York, 1947; *J. Am. Pharm. Assoc.*, **39,** 245 (1950).

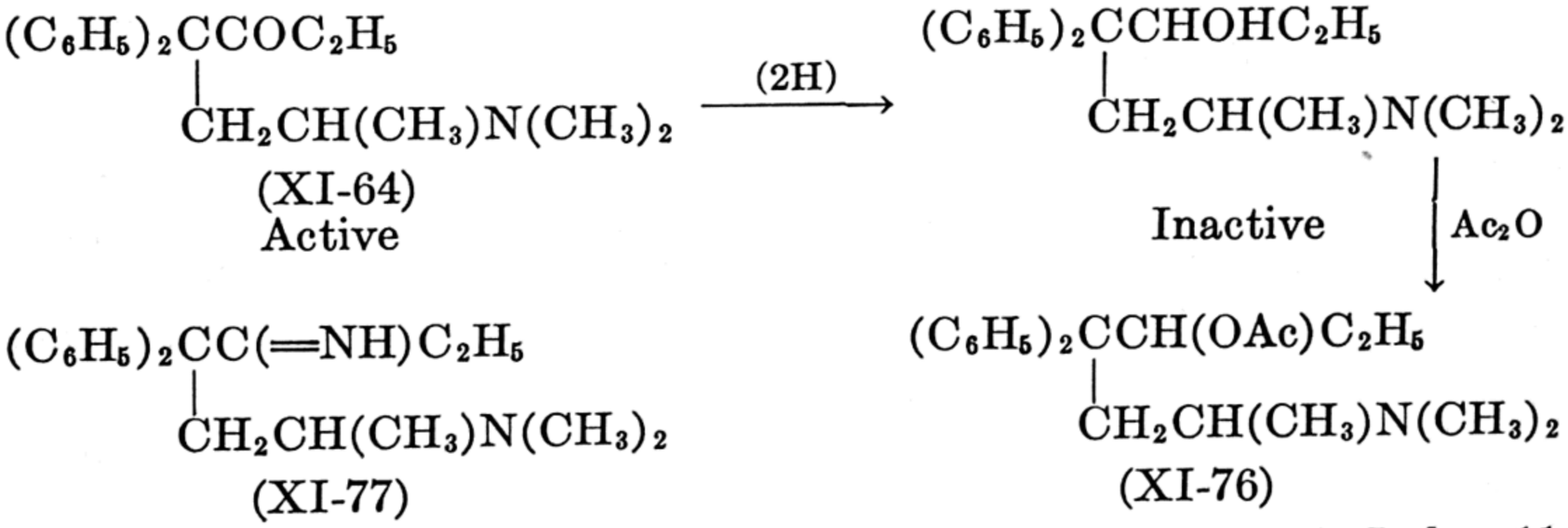
[52a] Elliot *et al.*, *J. Pharmacol. Exptl. Therap.*, **95,** 494 (1949).

in a compound which contains a morpholino group in place of the dimethylamino group. This compound has been introduced into therapy under the name of Heptazone (XI-75).[53] It is less toxic and more effective than methadon, and has not given any evidence of producing tolerance in laboratory animals.



(XI-75)

Reduction of methadon abolishes the morphine-like action of the drug but acetylation (XI-76) of the carbinol restores analgetic activity, and this is true also in a smaller degree when the ketimine (XI-77) of methadon is acetylated.

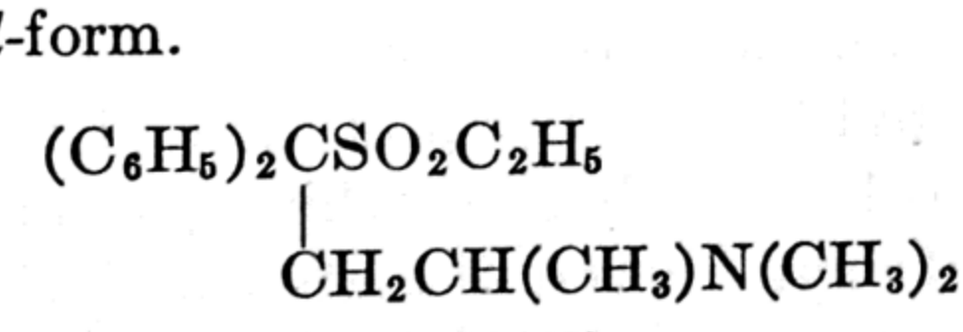


(XI-64)
Active

(XI-77)
Therapeutic Index 4

(XI-76)
Active, Therapeutic Index, 11

The replacement of the keto group of methadon by a sulfone group has been studied by Archer and Suter.[54] 1,1-Diphenyl-3-dimethylaminobutyl-ethyl sulfone (XI-78) is as potent as methadon and only one-half as toxic; the levorotatory form of the sulfone is twenty times more active as an analgetic than the *d*-form.



(XI-78)

[53] Wilson and Hunter, *Brit. Med. J.*, **1948,** 553. Basil, Edge, and Somers, *Brit. J. Pharmacol.*, **5,** 125 (1950).

[54] Klenk, Suter, and Archer, *J. Am. Chem. Soc.*, **70,** 3846 (1948). Tullar, Wetterau, and Archer, *ibid.*, **70,** 3959 (1948).

V. MORPHINAN DERIVATIVES

The closest synthetic approach to the structure of the morphine alkaloids is found in the synthesis of N-methylmorphinan (XI-79) and some of its derivatives by Grewe.[55] This compound constitutes the basic skeleton of the morphine derivatives without the ether bridge and may be regarded as related to the natural alkaloids as tropane is to cocaine or atropine. The synthesis of N-methylmorphinan was not only the first significant contribution to the age-old problem of synthesizing morphine, but has also been rewarded by the discovery that analgetic activity of the same order as in morphine resides in the ring system without outlying functional groups. Although this could be expected from the variations of the morphine structure which had demonstrated that at least the phenolic hydroxyl (in codeine) and the alcoholic hydroxyl (in desomorphine) are unnecessary for the production of analgetic activity, no des-phenolic derivative of morphine had ever been prepared. The activity of N-methylmorphinan now shows that none of the three oxygen functions are necessary for favorable pharmacological behavior.

The Grewe synthesis of morphinan starts from ethyl cyclohexanone-*o*-carboxylate (XI-80) which is condensed with ethyl cyanoacetate to (XI-81). Hydrolysis in acid solution furnishes 3,4,5,6-tetrahydrohomophthalic acid (XI-82) which yields the isoquinoline derivative (XI-83) on treatment with ammonia. Removal of the two hydroxyl groups by chlorination (XI-84) and reduction leads to 5,6,7,8-tetrahydroisoquinoline (XI-85) the methiodide of which, on treatment with benzylmagnesium chloride, gives 1-methyl-2-benzyl-1,2,5,6,7,8-hexahydroisoquinoline (XI-86). Hydrogenation of the 3,4-double bond produces (XI-87a) which is related to the 1-benzylisoquinoline alkaloids. If its formula is written as in (XI-87b) the possibility of closing a phenanthrene ring system becomes apparent. This ring closure has been realized by treating (XI-87) with phosphoric acid; the shift of the double bond under the influence of this reagent follows the pattern observed in other similar hydroaromatic cyclizations (Fig. 5).

An overall yield of 200 g. of N-methylmorphinan was obtained from 1 kg. of ethyl cyclohexane-*o*-carboxylate. The structure of the base was established rigidly by exhaustive methylation and degradation to 13-(β-dimethylaminoethyl) octahydrophenanthrene (XI-88). Since this compound was synthesized independently, and is most likely a derivative of *cis*-decalin, it appears probable that N-methylmorphinan also belongs in this steric series.

[55] Grewe, *Naturwissenschaften*, **11,** 333 (1946). *Chem. Ber.*, **81,** 279 (1948).

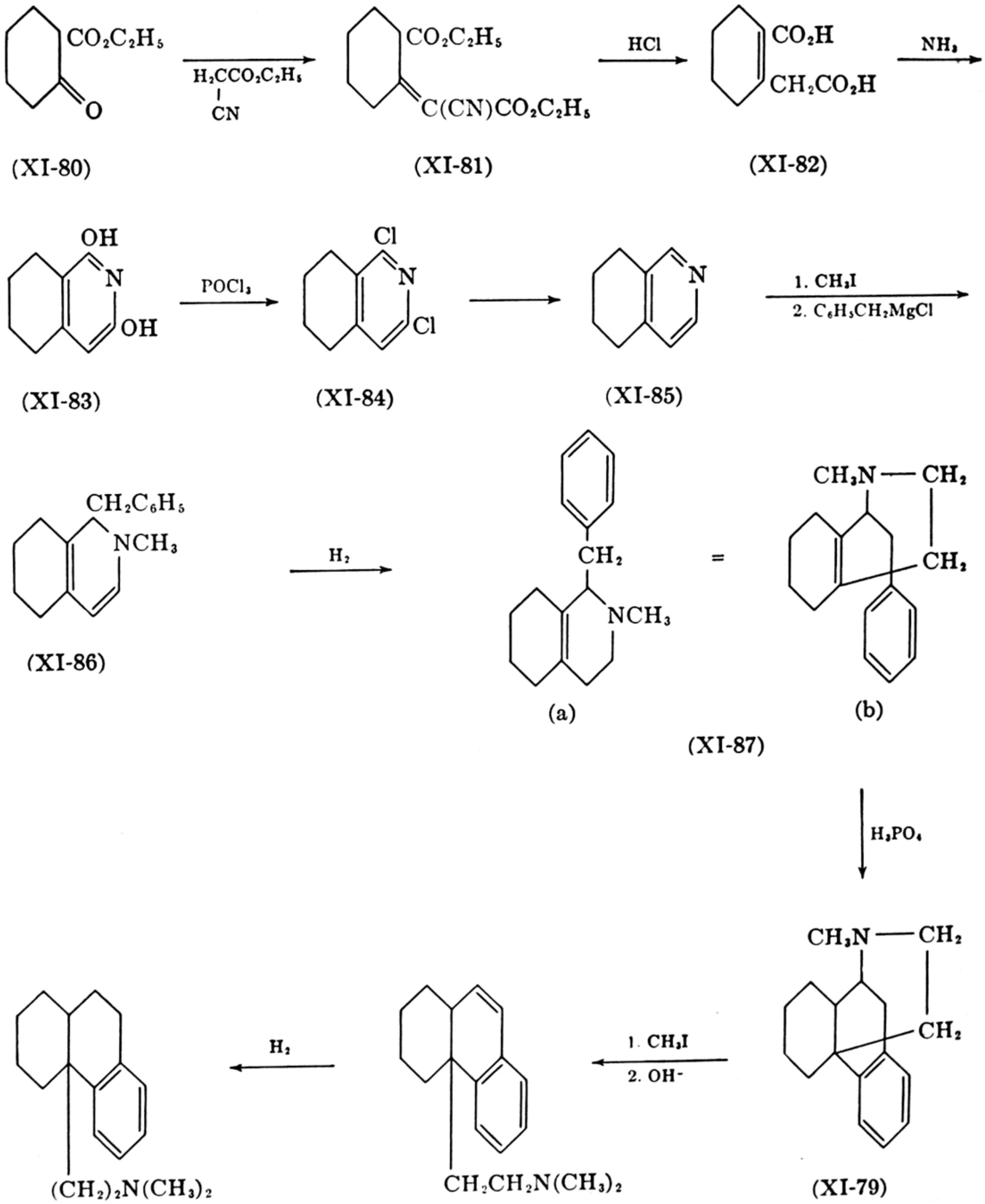
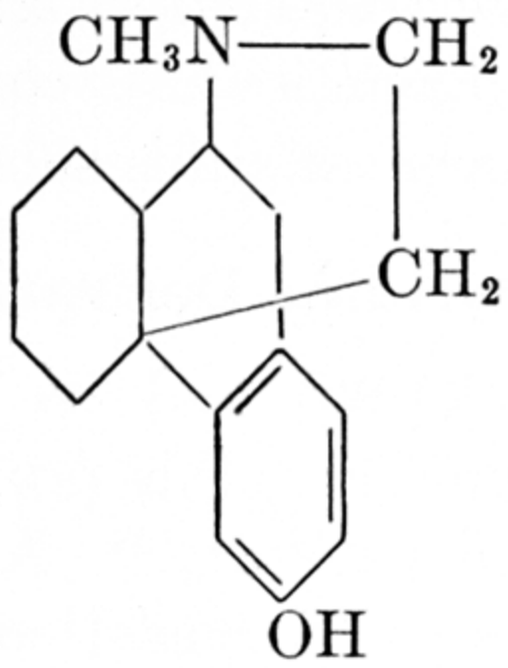


Figure 5. Synthesis and Degradation of N-Methylmorphinan[55]

Activity in man three times that of morphine has been observed with 3-hydroxy-N-methylmorphinan (XI-89)[56] which was synthesized by an

[56] Gross, Brotman, Magyfy, Sawtelle, and Zager, *Federation Proc.*, **8,** 297 (1949). Schnider and Grussner, *Helv. Chim. Acta*, **32,** 821 (1949). Schnider and Hellerbach, *ibid.*, *33*, 1437 (1950).

analogous route; it is 3 to 6 times as toxic as morphine. The 3-methoxy-4-hydroxy analog has recently also been synthesized.[56a] The resolved compound was identical with *d*-tetrahydrodesoxycodeine. Compound (XI-89)



(XI-89)

shows an even greater similarity to morphine than the desoxy derivative. It has been used successfully postoperatively, and in incurable carcinoma, and is said not to cause euphoria.

VI. OTHER SYNTHETIC ANALGETICS

It is not surprising that structures bearing groups similar to those found in morphine show some properties which are also exhibited by the parent alkaloid, but it should be remembered that such compounds must have certain physical characteristics which are necessary for their distribution in the tissues, their absorption, degradation and excretion. Only occasional hints pointing to a relation between chemical structure, physical properties, and pharmacological action in the series of analgetics may be found in the literature. Preiswerk[57] has suggested that morphine-like activity depends on a salt forming group which is necessary to make the compound soluble in water, and secondly, on a weakly acidic group such as the phenolic hydroxyl in morphine which may act as an anchoring group. Such groups are present both in the various phenanthrene, dibenzofuran, dibenzothiophene, carbazole and other amino alcohols as well as in the Demerol and methadon types, where at least the electron attracting aromatic rings may be regarded as the weakly anchoring groups.

It has been assumed that the Meyer-Overton theory of distribution between lipids and blood would hold for analgetics as well as for other central depresssants, but no accurate studies in this direction have been made. It would be highly desirable to study the relation of several chemical or physical factors such as the distribution coefficient, the surface tension, adsorption, acidity, colloidal flocculation, etc. and compare their inter-

[56a] Grewe, Mondon, and Nolts, *Angew. Chem.*, **61,** 442 (1949); Randall and Lehmann, *J. Pharmacol. Exptl. Therap.*, **99,** 163 (1950).

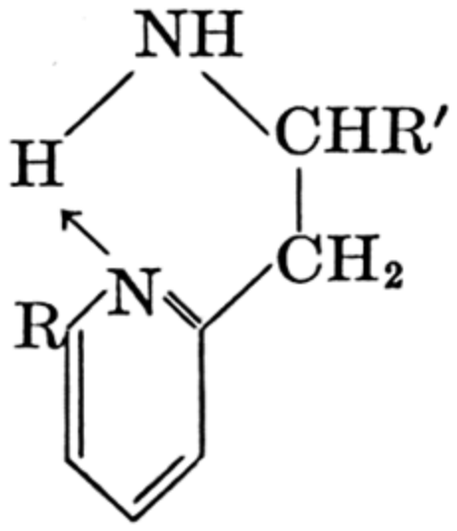
[57] Preiswerk, in *Festschrift Emil Barell*, Roche Co., Basel, **1936,** p. 185.

dependence with the pharmacological efficacy within a specific group of analgetics.

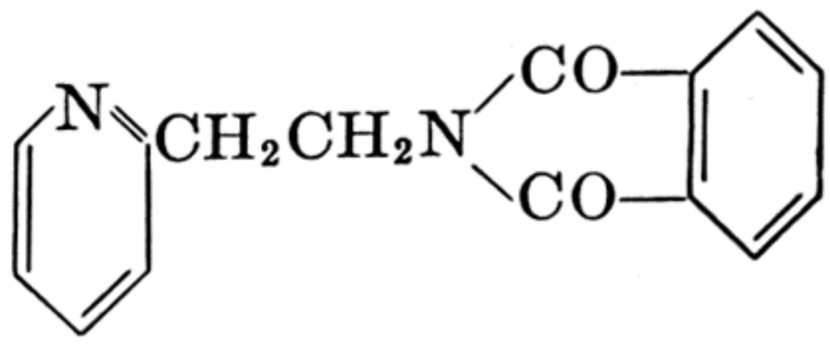
The analgetic activity of structurally simple compounds could be raised to a useful level if the frequently high toxicity of such materials could be lowered. Many analgetics are convulsants at relatively low dosages, and an attempt to overcome this shortcoming is described below.

1. Pyridine Derivatives

2-β-Pyridylethylamine (XI-90) and its homolog (XI-91) are convulsants of the histamine type, and this property may be attributed to their ability to exist in a chelated form.[58] A methyl group in 6-position might be expected to interfere with chelation by calling upon the cyclic nitrogen for a tautomeric shift, and thus the "toxicity", i.e. the histamine-type activity should be somewhat decreased.[59] β-(6-Methyl-2-pyridyl) isopropylamine (XI-92) actually shows marked analgesia at the 7 mg./kg. level but its still unfavorable therapeutic index (1:3) has prevented further studies. Even 2-[2-(phthalimido)ethyl]pyridine (XI-94) shows mild analgetic activity.[59a]



R = H; R′ = H: (XI-90)
R = H; R′ = CH_3: (XI-91)
R = CH_3; R′ = CH_3: (XI-92)



(XI-94)

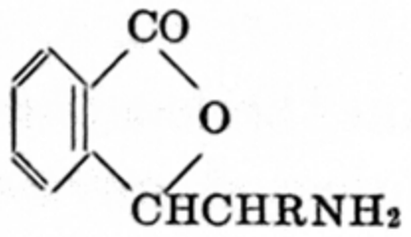
The discovery of the analgetic properties of this pyridylisopropylamine ties in with the activity of simple compounds containing the β-arylethylamine structure. In the series of phenalkylamines a steady increase of activity has been noted from β-phenylisopropylamine ($C_6H_5CH_2$-$CH(CH_3)NH_2$) to 5-phenyl-2-aminopentane ($C_6H_5(CH_2)_3CH(CH_3)NH_2$). Further separation of the aromatic ring and the primary amino group results in a sharp decrease of activity (Chapter XIX).

[58] Niemann and Hays, *J. Am. Chem. Soc.*, **64,** 2288 (1942).
[59] Burger and Ullyot, *J. Org. Chem.*, **12,** 342 (1947).
[59a] Kirchner and Cavallito, U. S. Pat. 2,498,497 (1950).

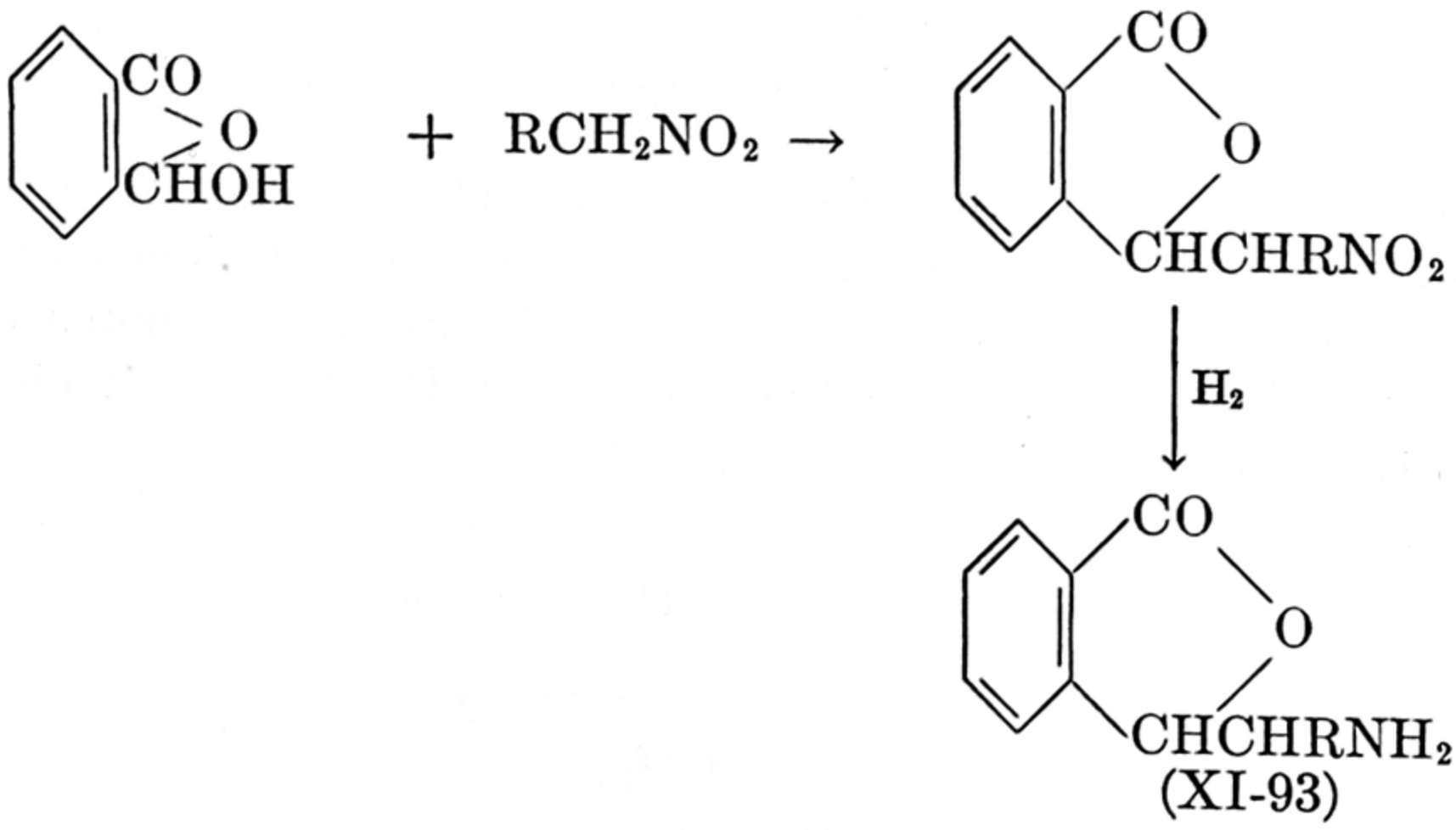
2. Phthalidyl Aminoalkanes

Since pressor amine structure can elicit analgetic properties, it was only natural to search in similar compounds for a comparable or perhaps enhanced ability to relieve pain. While looking for a combination of vasoconstrictor and local anesthetic properties in compounds containing the characteristic features of pressor type amino alcohols, $C_6H_5CHOHCHRNH_2$,

TABLE VII. PHARMACOLOGICAL BEHAVIOR OF AMINOPHTHALIDYLALKANES[60]

	Dosage intraperitoneally, mg./kg.	Analgesia	Toxicity
R = CH_3	100–250	±	±
C_2H_5	75–250	++	−
C_3H_7	50–100	±	+
C_4H_9	25–75	±	+
C_5H_{11}	50–75	±	+

and the amino alcohol benzoate structure, $C_6H_5COO(CH_2)_nNR_2$ found in so many local anesthetics, certain aminophthalidylalkanes (XI-93) were studied for possible analgetic effects. Some of these compounds, synthesized from phthalaldehydic acid and nitroalkanes with subsequent reduction of the condensation products caused marked analgesia in laboratory animals.[60]



(XI-93)

[60] Ullyot, Stehle, Zirkle, Shriner, and Wolf, *J. Org. Chem.*, **10,** 429 (1945).

3. Ethanol

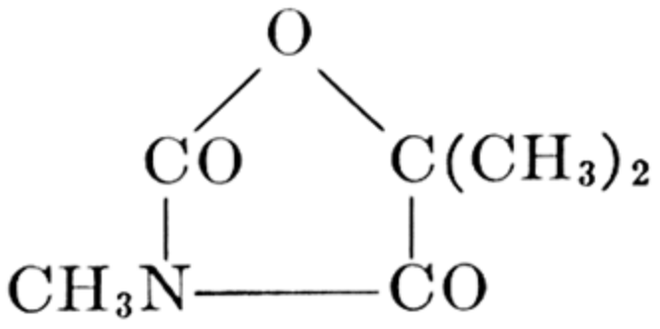
Among the structurally simplest substances which, when applied properly, exert a powerful analgetic action is ethyl alcohol which had been used for the obtusion of surgical pain before the advent of modern anesthetics. Injected into nerves or nerve ganglia in small amounts, alcohol brings rapid, and often long-lasting relief from pain caused by angina pectoris, pelvic carcinoma and other intractable conditions.

4. Diethylaminoethanol

Of great practical importance is the discovery that the local anesthetic procaine (p-$H_2NC_6H_4COOCH_2CH_2N(C_2H_5)_2$) when injected intravenously has powerful and prolonged analgetic activity in post-operative application. An even more pronounced effect without any toxic side-actions can be obtained by intravenous administration of 2-diethylaminoethanol. Also, diethylaminoethanol appears to have analgetic properties when given orally or intramuscularly.[61]

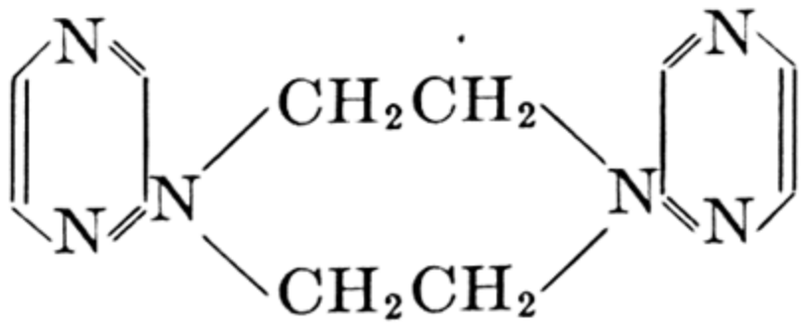
5. Tridion

The recent chance discovery of the excellent analgetic activity of 3,5,5-trimethyloxazolidine-2,4-dione[61] (Tridion, XI-95) has lent weight to



(XI-95)

the hope of finding further useful drugs among relatively simple compounds. This is also shown by the observation that certain 1,4-diheterocyclically substituted derivatives of piperazine, originally prepared as potential anticonvulsants, have pronounced activity. 1,4-Di-(2-pyrazyl) piperazine (XI-96) is extremely active as an analgetic.[62]



(XI-96)

[61] Rovenstine, in "Newer Synthetic Analgesics," *Ann. N. Y. Acad. Sci.*, **51,** 145 (1948).

[62] Denton, U. S. Pat. 2,459,367 (1949).

VII. THE ANTIPYRETIC-ANALGETICS

Many drugs have been tested for both antipyretic and analgetic activity. A compound which is an antipyretic is in general an analgetic and vice versa, and depressant effects accompany both types of activity. The antipyretic effect of many hypnotics ties in with these observations. Antipyretic drugs do not lower normal body temperatures appreciably but set the "thermostat" in the hypothalamus back to normal in a feverish organism. Testing for antipyretic effects may be carried out in mice or rabbits made feverish by subcutaneous injections of hay infusions.

Work in the field of antipyretic analgetics has been inactive for some time because modern clinicians are using fever as a therapeutic aid in overcoming infections which do not respond to drugs. The significance of fever for the natural defenses of the body is not well understood, and there is a tendency not to interfere with these physiological mechanisms. However, the work with antipyretics in the past illustrates the tendency of certain periods to favor specific structures in a drug, and to abandon these structures later in favor of other systems without a compelling pharmacological reason.

Recent studies have cast doubts on the intrinsic analgetic value of orally administered antipyretics. By present standards, none of them alter significantly the normal pain thresholds.[63] However, it is possible that the discrepancies found in the analgetic activity of these drugs are due to the inability of present test methods to pick up analgetic values of a low order.

1. Pyrazolone Derivatives

In the field of pyrazolone derivatives, the period from 1890 to 1920 was particularly fruitful. It was opened by the discovery of Knorr[63a] that a compound to which he had attributed faultily a quinine-like structure was actually a pyrazolone derivative. He called it antipyrine and found it to have a strong febrifuge action even before its correct chemical structure had been ascertained. Subsequent to this finding, many other derivatives of pyrazolone were prepared and tested primarily for antipyretic activity but incidentally also for analgetic and other effects. In this group of compounds, Pyramidon (aminopyrine, XI-96) and Knorr's original antipyrine (XI-97) have been most successful. Table VIII shows a few of the hundreds of compounds in an arbitrary selection. They are those derivatives which have been found of particular interest at the time of their dis-

[63] Sonnenschein and Ivy, *J. Pharmacol. Exptl. Therap.*, **97,** 308 (1949).
[63a] Knorr, *Ber.*, **16,** 2597 (1883); **17,** 2037 (1884); *Ann.*, **238,** 137, 160, 203 (1887).

TABLE VIII. PYRAZOLONE DERIVATIVES

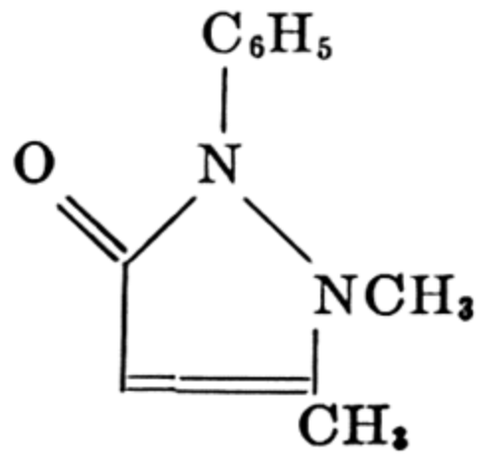
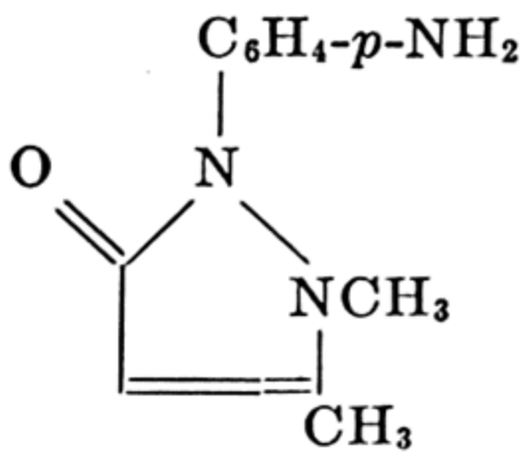
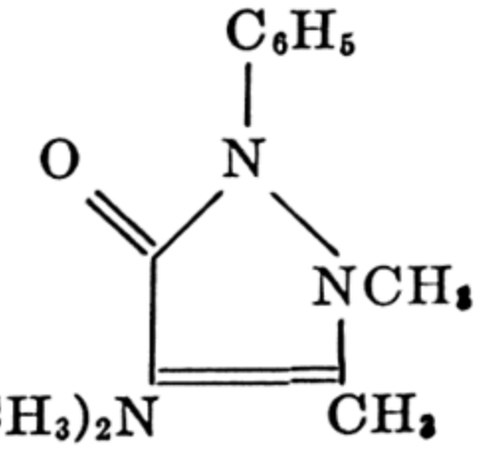
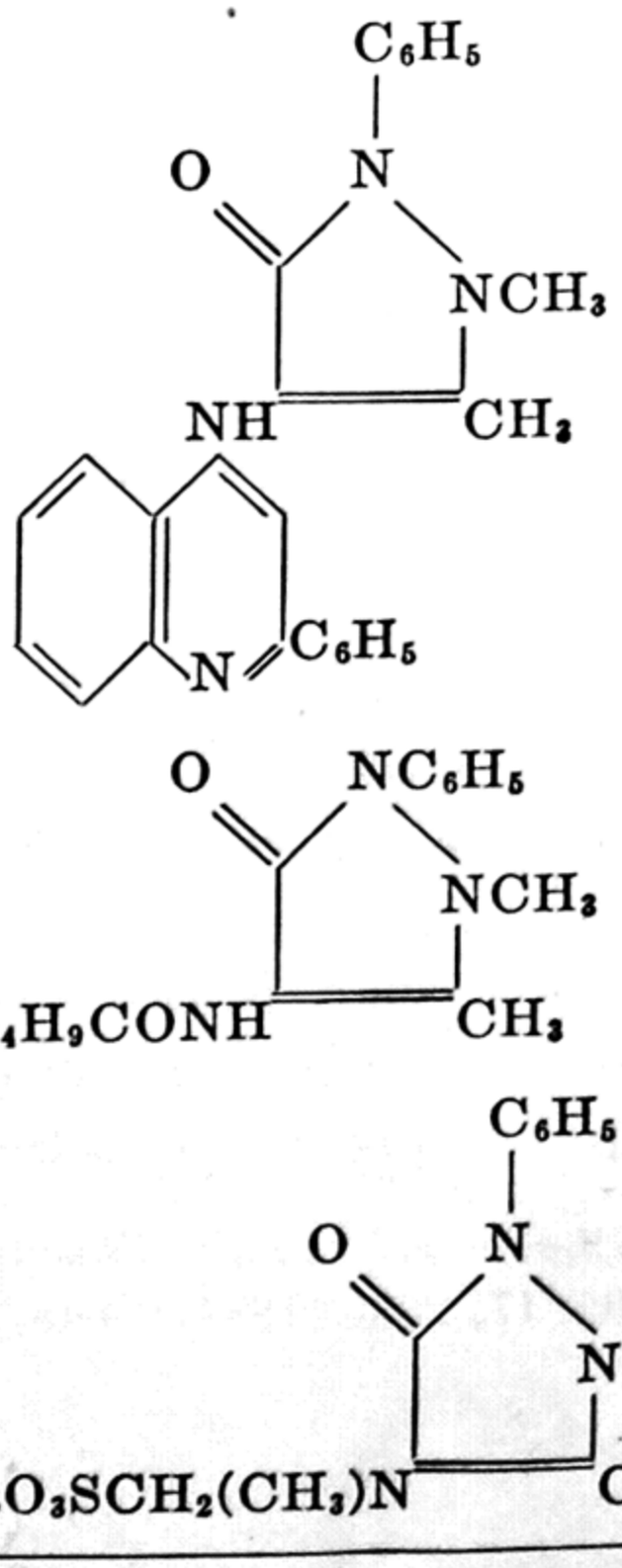
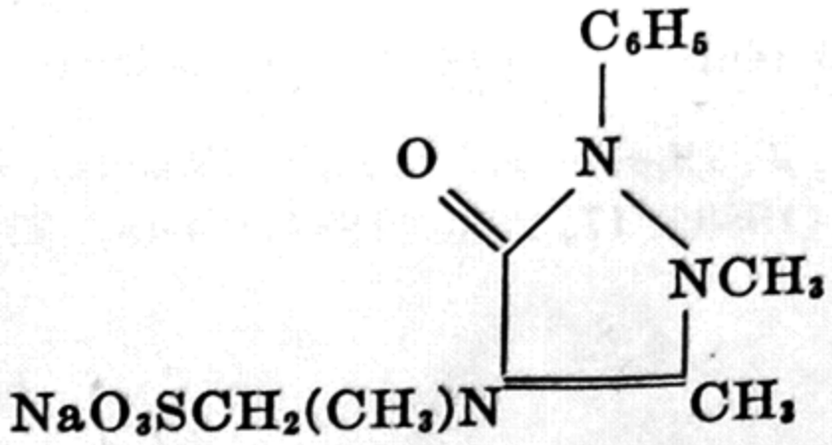
Name	Formula	Antipyresis	Analgesia	Toxicity
1-Phenyl-2,3-dimethyl-5-pyrazolone (Antipyrin, Analgesin)		++	++	+
1-(4-Aminophenyl)-2,3-dimethyl-5-pyrazolone		++	++	±
1-Phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone (Aminopyrin, Pyramidon)		+++	+	+
1-Phenyl-2,3-dimethyl-4-(2-phenyl-4-quinolyl) amino-5-pyrazolone				+
1-Phenyl-2,3-dimethyl-4-valeramido-5-pyrazolone (Neopyrine)		++		±
Sodium 1-Phenyl-2,3-dimethyl-5-pyrazolone-4-methylaminomethane sulfonate (Novalgin)		++	+	

Table continued

TABLE VIII (*Continued*)

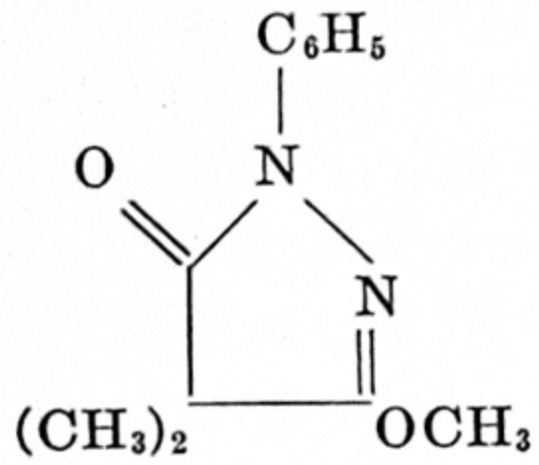
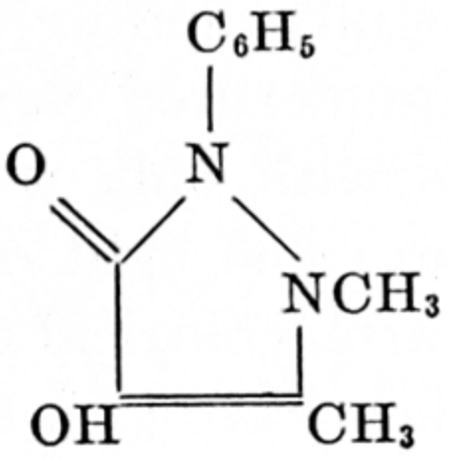
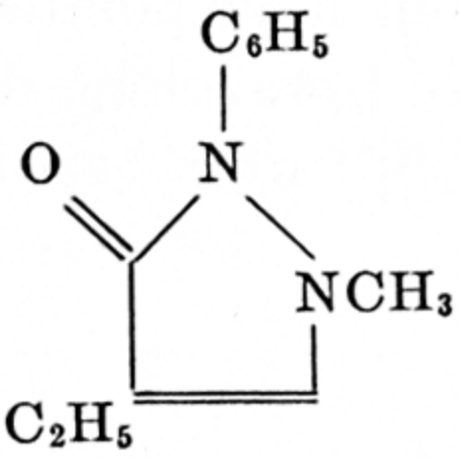
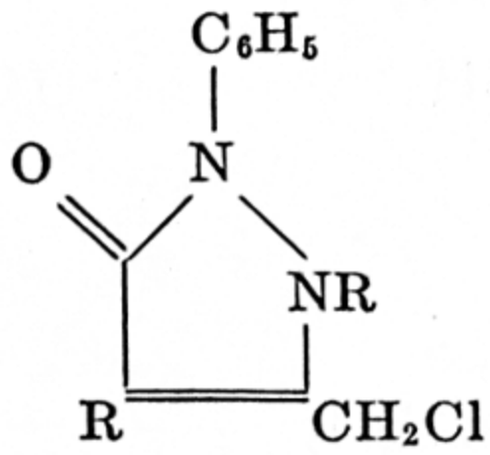
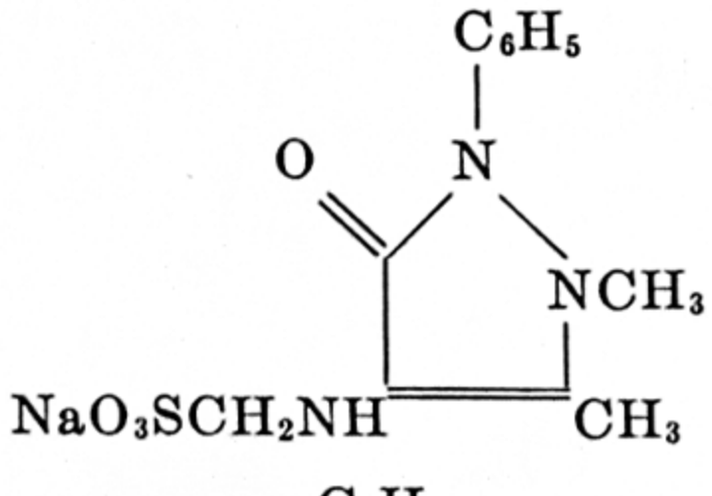
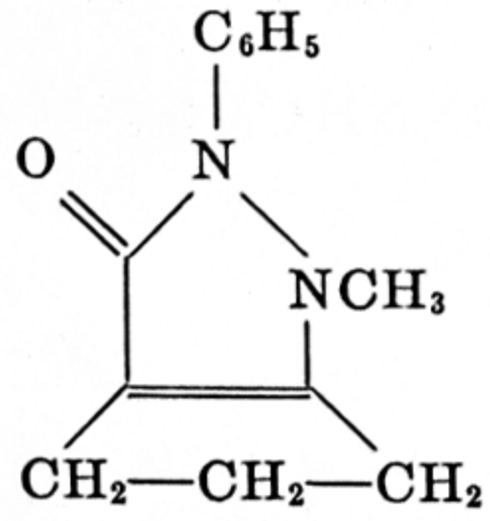
Name	Formula	Antipyresis	Analgesia	Toxicity
1-Phenyl-3-methoxy-4,4′-dimethyl-5-pyrazolone		+		
1-Phenyl-2,3-dimethyl-4-hydroxy-5-pyrazolone		++		
1-Phenyl-2-methyl-4-ethyl-5-pyrazolone		++		±
1-Phenyl-2,4-dialkyl-3-halogenomethyl-5-pyrazolone		+		
1-Phenyl-2,3-dimethyl-4-sulfomethylamino-5-pyrazolone (Melubrin)		+	++	±
1-Phenyl-2-methyl-3,4-cyclotrimethylene-5-pyrazolone[67]		++	++	
Aminopyrine and Trichloroethylurethan (Compral)			++	

TABLE VIII. PYRAZOLONE DERIVATIVES

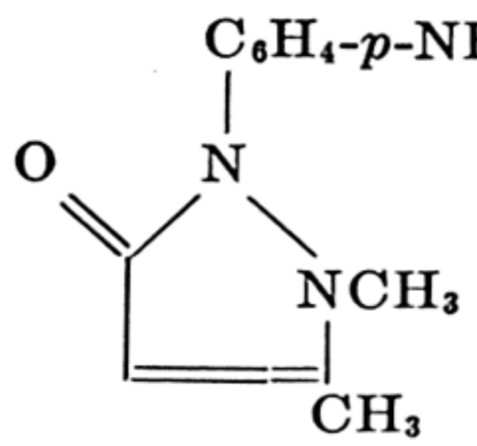
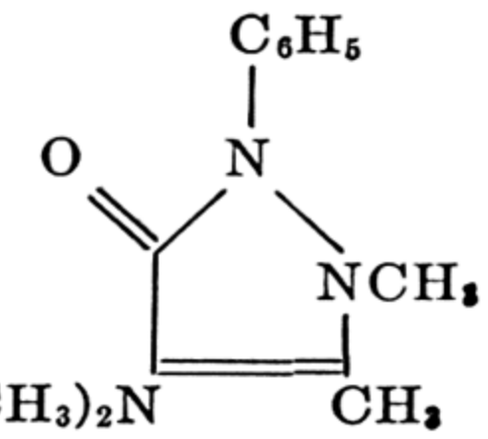
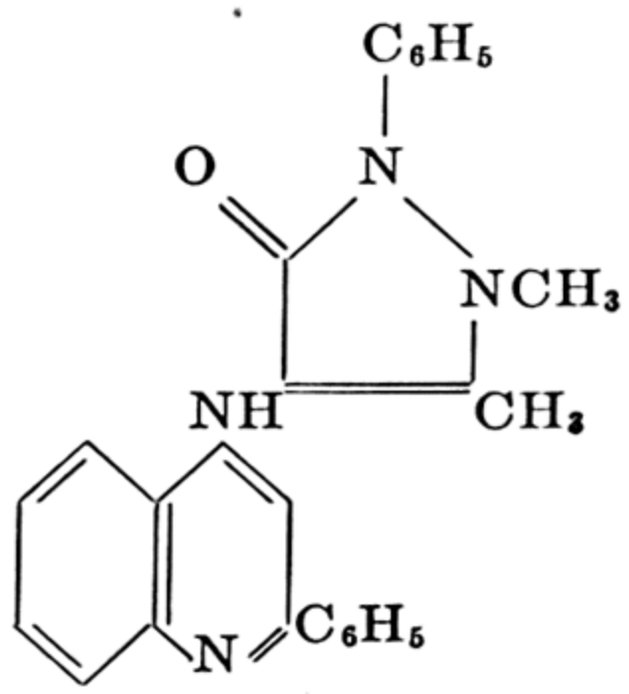
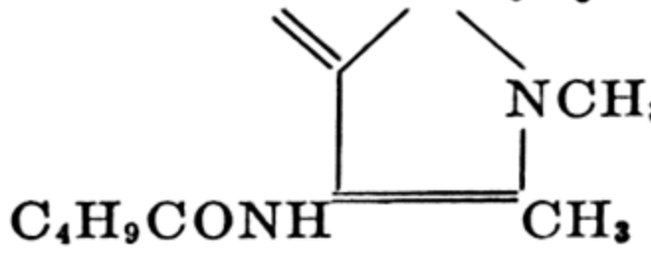
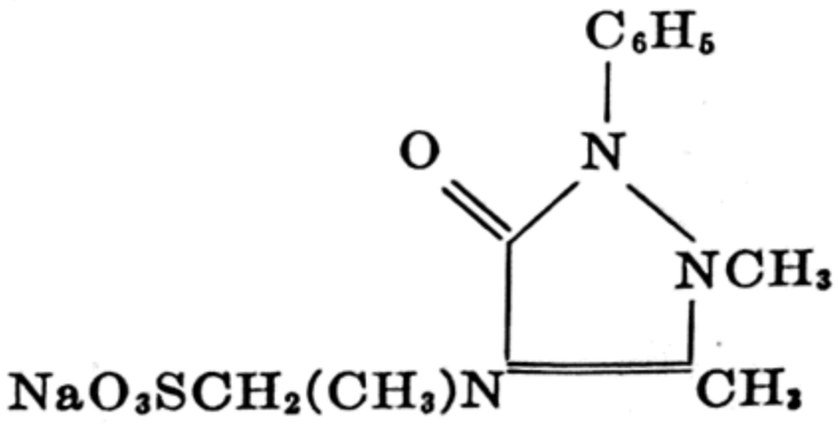
Name	Formula	Antipyresis	Analgesia	Toxicity
1-Phenyl-2,3-dimethyl-5-pyrazolone (Antipyrin, Analgesin)		++	++	+
1-(4-Aminophenyl)-2,3-dimethyl-5-pyrazolone		++	++	±
1-Phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone (Aminopyrin, Pyramidon)		+++	+	+
1-Phenyl-2,3-dimethyl-4-(2-phenyl-4-quinolyl) amino-5-pyrazolone			+	
1-Phenyl-2,3-dimethyl-4-valeramido-5-pyrazolone (Neopyrine)		++		±
Sodium 1-Phenyl-2,3-dimethyl-5-pyrazolone-4-methylaminomethane sulfonate (Novalgin)		++	+	

Table continued

TABLE VIII (*Continued*)

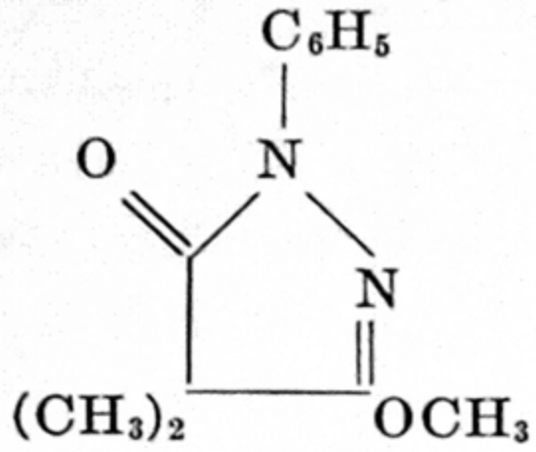
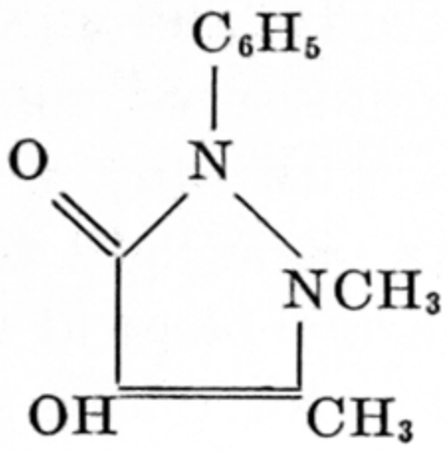
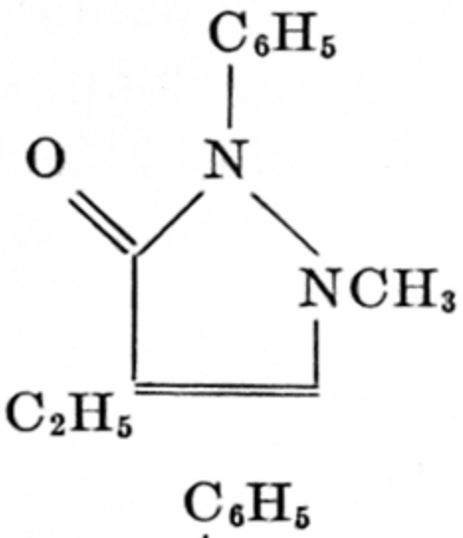
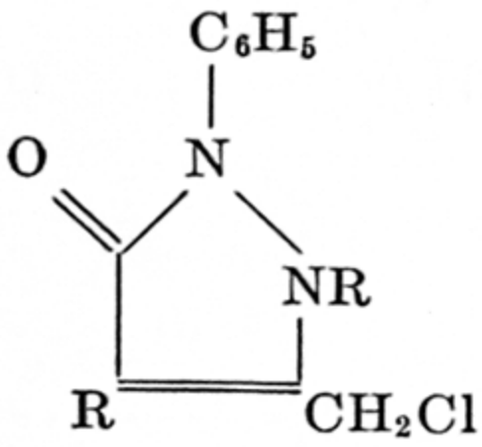
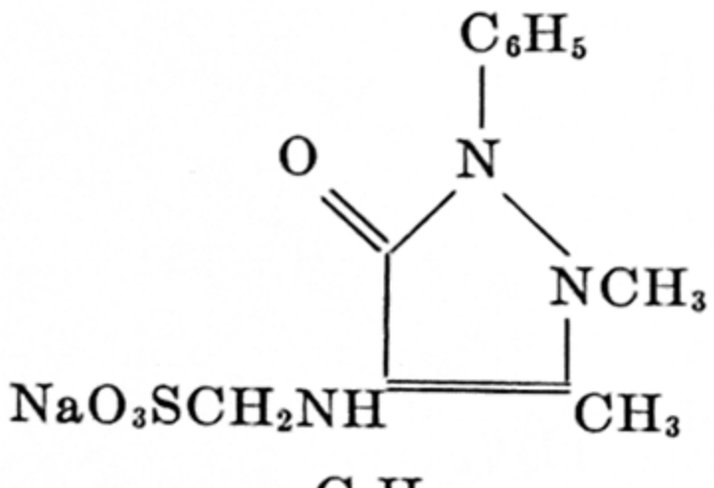
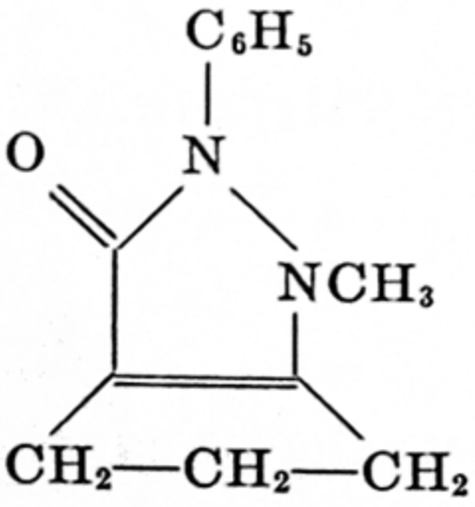
Name	Formula	Antipyresis	Analgesia	Toxicity
1-Phenyl-3-methoxy-4,4′-dimethyl-5-pyrazolone		+		
1-Phenyl-2,3-dimethyl-4-hydroxy-5-pyrazolone		++		
1-Phenyl-2-methyl-4-ethyl-5-pyrazolone		++		±
1-Phenyl-2,4-dialkyl-3-halogenomethyl-5-pyrazolone		+		
1-Phenyl-2,3-dimethyl-4-sulfomethylamino-5-pyrazolone (Melubrin)		+	++	±
1-Phenyl-2-methyl-3,4-cyclotrimethylene-5-pyrazolone[67]		++	++	
Aminopyrine and Trichloroethylurethan (Compral)			++	

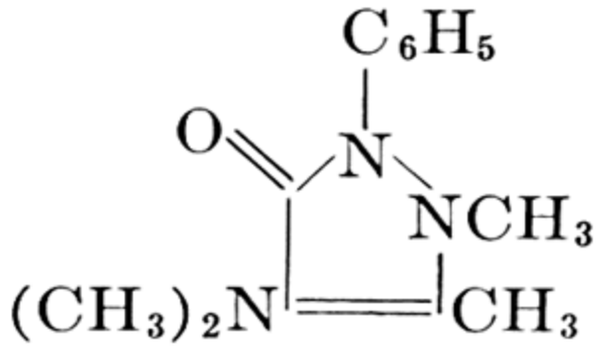
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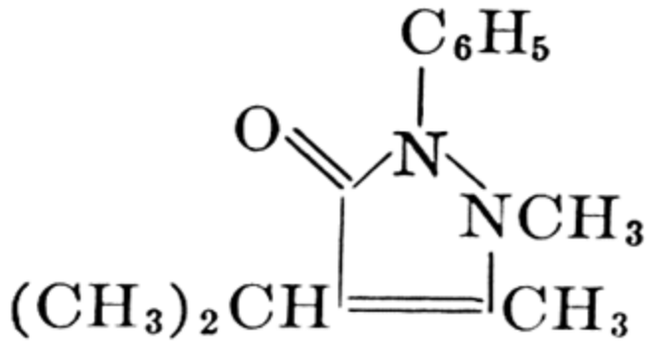
Name	Formula	Antipyresis	Analgesia	Toxicity
Aminopyrine and Isopropylphenylbarbituric acid (Allonal)		+	+	±
2 Aminopyrine + 1 Diethylbarbituric acid (Veramon)		+	+	±

covery and pharmacological study, and among them are some of the compounds which have been manufactured commercially in the past. There have been many compounds with only a low antipyretic and analgetic rating whose structure throws some light on the rather vague connection of chemical structure and pharmacological activity in this series, but they have been omitted because they have long since gone into oblivion.

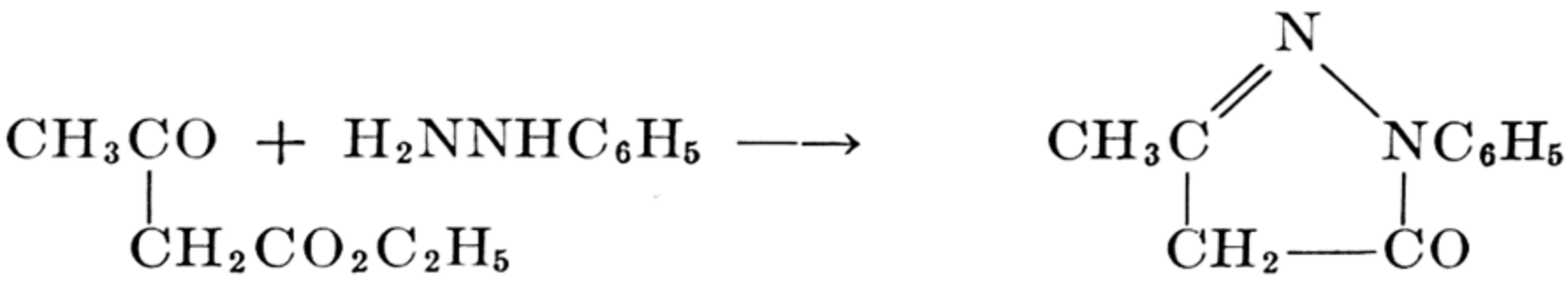
Two valuable observations have pointed the way to a more purposeful pursuit of synthesis of active pyrazolone derivatives. One is the experiment by Erlenmeyer and Willi[64] who, based on the thesis of isosterism re-



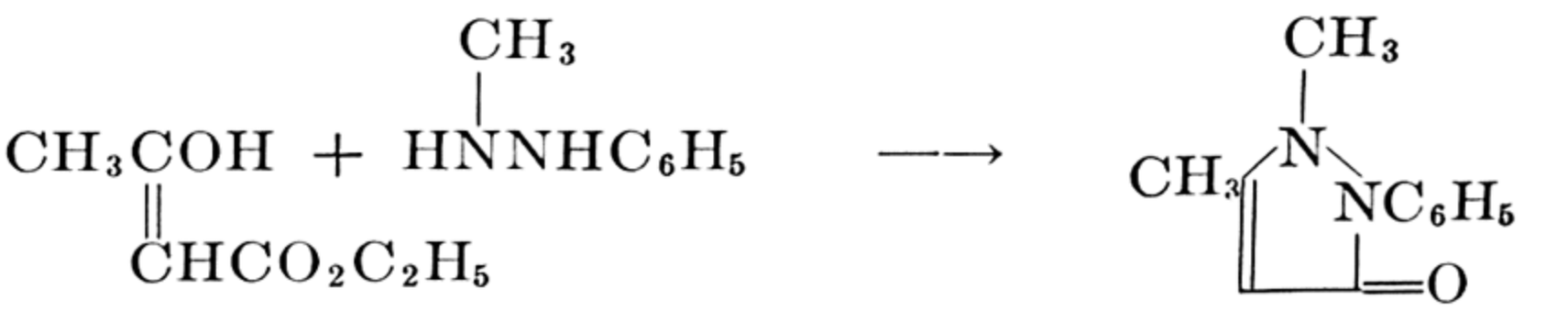
(XI-96)



(XI-98)



(XI-99)



(XI-97)

[64] Erlenmeyer and Willi, *Helv. Chim. Acta*, **18,** 740 (1935).

placed the dimethylamino group in aminopyrine (XI-96) by an isopropyl group and obtained a successful antipyretic drug (XI-98).

The other interesting phenomenon is the synergism of pyrazolone derivatives and hypnotics. Veramon, Compral, and Allonal are examples for this drug combination. Veramon consists of two moles of aminopyrine and one mole of diethyl barbituric acid. Its antipyretic effect is greater than that of the corresponding amount of aminopyrine alone. The explanation of this phenomenon is difficult since diethyl barbituric acid has no pronounced antipyretic action itself. However, it is a depressant and may thereby influence the body temperature.

Syntheses of medicinal derivatives of pyrazolone may be illustrated for antipyrine and aminopyrine. Antipyrine (XI-97) is prepared by condensing phenylhydrazine with ethyl acetoacetate, and methylating the resulting phenyl-methylpyrazolone (XI-99). Alternately, N-methylphenylhydrazine can be condensed with ethyl acetoacetate with comparable results.

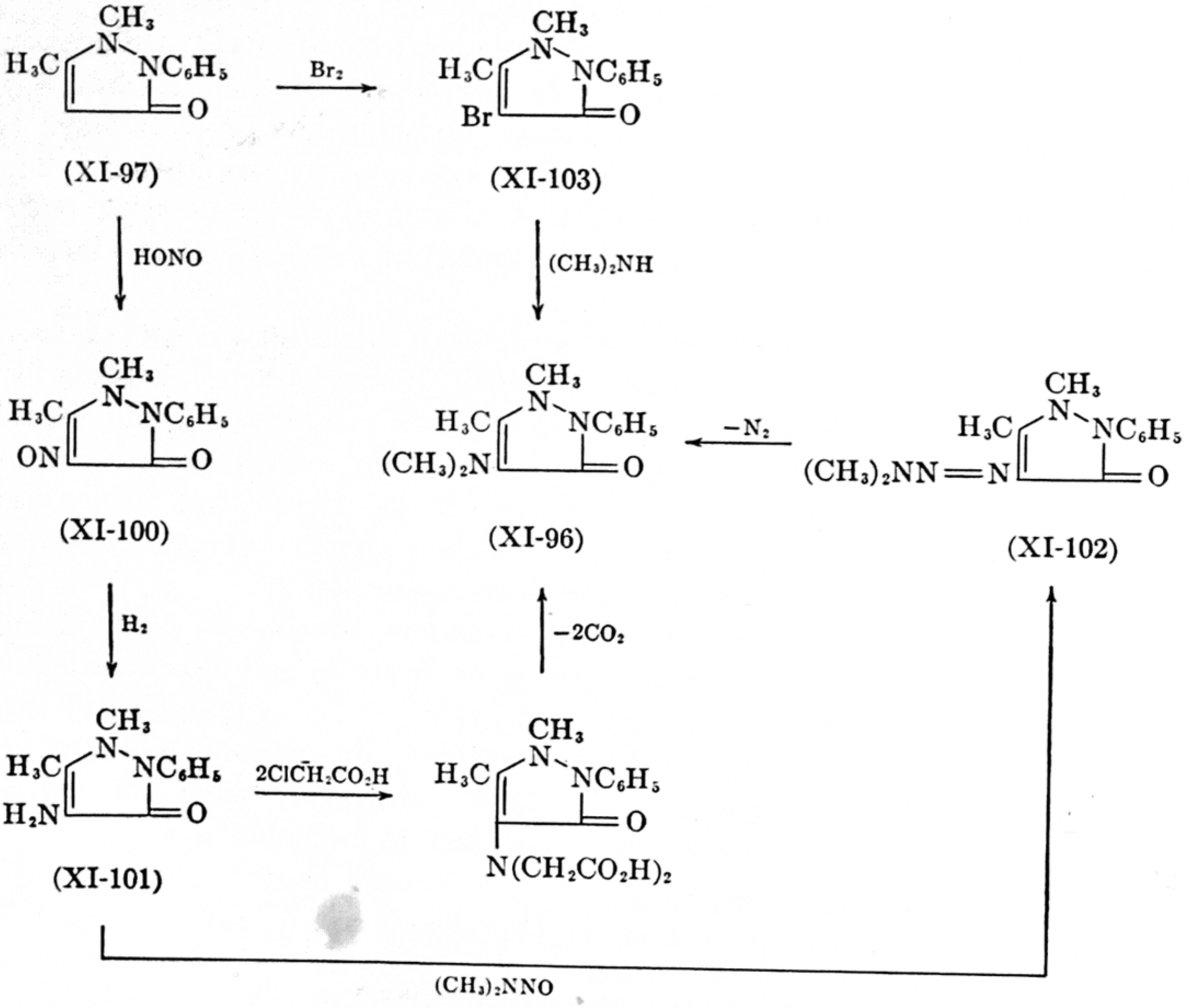


Figure 6. Syntheses of Aminopyrine

The dimethylamino group of aminopyrine (XI-96) can be introduced into the molecule of antipyrine by way of the isonitroso derivative (XI-100) and aminoantipyrine (XI-101). The latter can be methylated by preparing its diacetic acid derivative and decarboxylating, or by diazotizing aminoantipyrine with nitrosodimethylamine and eliminating nitrogen from the diazo compound (XI-102). One can also brominate antipyrine, and replace the bromine atom of 4-bromoantipyrine (XI-103) which is activated by the α-carbonyl group, with the dimethylamino radical.

2. Derivatives of Aniline and Aminophenol

Although aniline is a toxic amine and has to be excreted from the animal organism by biological oxidation and conjugation, acetanilide which is reasonably easily hydrolyzed to aniline in the organism exerts a strong antipyretic and analgetic effect. Even though its toxicity is considerable, acetanilide has become the active ingredient of many "patent" medicines and headache nostrums under the name of antifebrin[65] and is still used widely by the public for the relief of headache and other neuralgias.

The most pronounced toxic symptom caused by aromatic amines and their derivatives is formation of methemoglobin. Methemoglobin is a chocolate-colored oxyhemoglobin in which the heme has been oxidized to the ferric stage, and which no longer delivers oxygen for respiration. The aniline derivatives (acetanilide, etc., sulfanilamide) interfere with enzymatic carriers which would permit reconversion of the ferric to the ferrous form.

In the course of a search for a better drug in this group, it was realized that the biological oxidation product of aniline, *p*-aminophenol, is probably the carrier of the toxic action of aniline. If the *p*-hydroxyl group could be blocked, especially in an anilide, a safer analgetic and antipyretic might result. This prediction was borne out when it was found that ethers and certain esters of *p*-aminophenol have a higher pharmacological potency without some of the side effects of the parent compound.

The most successful of these compounds is Acetophenetidine (phenacetin) which is recommended as a strong antipyretic and antineuralgic.[66] It is said to be perhaps the least toxic antipyretic. Other members of this series have an equal or sometimes higher activity, for instance, methacetin, phenocoll, *p*-allyloxyacetanilide and others. However, their low therapeutic index has made it inadvisable to use them in medicine.

[65] Cahn, *Centr. Klin. Med.*, **7,** 561 (1886).
[66] Hinsberg and Kast, *Centr. Klin. Med.*, **25,** 145 (1887).
[67] Mannich, *Arch. Pharm.*, **267,** 699 (1929).
[68] Hambourger, *Proc. Soc. Exptl. Biol. Med.*, **31,** 365 (1933).
[69] Cox, Eckler, and Shriner, *J. Am. Chem. Soc.*, **53,** 3498 (1931).

The chemical criterion of all the active drugs has been the relative ease of hydrolysis of the anilide group. Other structural groups which can be converted to aromatic amino groups by plausible biological reactions may be responsible for the analgetic activity of certain compounds. The linkage between the two nitrogen atoms in phenylhydrazine and phenylsemicarbazide derivatives is reduced readily, and the potential conversion to aniline may account for the usefulness of some of these drugs. Phenylsemicarbazide (XI-104) is used as an antineuralgic in South America, and cryogenin (see Table IX) is supposed to have the most favorable properties of this group. The aromatic semicarbazides are prepared from arylhydrazines and alkali cyanates or urea:

$$C_6H_5NHNH_2 + HCNO \rightarrow C_6H_5NHNHCONH_2$$

(XI-104)

In this general group, the aromatic urethans should also be mentioned. Urethan itself has been recommended as a hypnotic but its toxicity is prohibitive; analgetic activity is not exhibited by this compound in doses up to 40 milligrams per kilogram in rats. Phenylurethan (euphorine), its N-methyl- and *p*-hydroxy derivatives, are still used occasionally. Phenylurethan (XI-105) is prepared from aniline and ethyl chloroformate.

$$C_6H_5NH_2 + ClCOOC_2H_5 \rightarrow C_6H_5NHCOOC_2H_5$$

(XI-105)

It should be noted that in the Tables of this Section, analgetic activity may mean antineuralgic action while "general depression" is a summary of the narcotic and hypnotic properties of the drug. The more modern comprehensive terms have been chosen as headings although some of the older testing methods actually revealed antineuralgic and hypnotic activity. As in the Table of pyrazolone derivatives (Table VIII), Table IX also only includes some of the compounds which have shown pronounced activity or are otherwise of pharmacological interest. Hundreds of compounds which have been prepared but for which no pharmacological tests have been recorded have been omitted from this selection.

Table IX follows on pages 198 and 199.

TABLE IX. DERIVATIVES OF ANILINE

Name	Derivative of Benzene	Synonym	Antipyresis	Analgesia	Depression	Toxicity
Acetanilide	—$NHCOCH_3$	Antifebrin	++	++		1:6.5
N-Methylacetanilide	—$N(CH_3)COCH_3$	Exalgin	++			+
Sulfacetanilide	—$NHCOCH_2SO_3H$		+			
4-Ethoxyacetanilide	1-$NHCOCH_3$, 4-OC_2H_5	Acetophenetidine Phenacetin	++	++	+	±
4-Methoxyacetanilide	1-$NHCOCH_3$, 4-OCH_3	Methacetin	+++	+++	+	+
4-Propoxyacetanilide	1-$NHCOCH_3$, 4-OC_3H_7		±			+
p-Aminophenol	1-OH, 4-NH_2					+
4-Acetamidophenol	1-OH, 4-$NHCOCH_3$		++	++	±	+
4-N-Ethylacetamidophenol	1-OH, 4-$N(C_2H_5)COCH_3$		−	−	−	−
N-Methyl-N-Acetylphenetidine	1-OC_2H_5, 4-$N(CH_3)COCH_3$	Methylphenacetin	−	++	++	−
N-Ethyl-N-Acetylphenetidine	1-OC_2H_5, 4-$N(C_2H_5)COCH_3$	Ethylphenacetin	±		++	−
N-Propyl-N-Acetylphenetidine	1-OC_2H_5, 4-$N(C_3H_7)COCH_3$	Propylphenacetin			±	
N-Benzylphenetidine	1-OC_2H_5, 4-$NHCH_2C_6H_5$		+			−
N-Ethyl-N-Sulfomethylphenetidine	1-OC_2H_5, 4-NCH_2SO_3H (with C_2H_5 on N)		+			
N-Aminoacetylphenetidine	1-OC_2H_5, 4-$NHCOCH_2NH_2$	Phenocol	++	++		
N-Propionylphenetidine	1-OC_2H_5, 4-$NHCOC_2H_5$	Triphenin	+	+	−	±
N-Lactylphenetidine	1-OC_2H_5, 4-$NHCOCHOHCH_3$	Lactophenin	+	++		
N-Ethylsulfonyl phenetidine	1-OC_2H_5, 4-$NHSO_2C_2H_5$		−	−	+	−
4-Isopropoxyacetanilide	4-$OCH(CH_3)_2$, 1-$NHCOCH_3$			+		
4-β-Hydroxyethylacetanilide	4-OCH_2CH_2OH, 1-$NHCOCH_3$	Pertonal	+		±	±

Name	Derivative of Benzene	Synonym	Antipyresis	Analgesia	Depression	Toxicity
4-Allyloxyacetanilide	4-$OCH_2CH{=}CH_2$, 1-$NHCOCH_3$		++	+	++	+
p-Phenetidine-N-glucoside	1-OC_2H_5, 4-$NHC_6H_{11}O_5$		+			−
(3-Methoxy-4-carbethoxy-benzal) *p*-phenetidine	1-OC_2H_5, 4-N=CH-C$_6$H$_3$(-$OCO_2C_2H_5$)(-OCH_3)	Eupyrine	±			−
Fural-*p*-phenetidine	1-OC_2H_5, 4-N=CHC_4H_3O		+			−
N-Acetyl-2-Methyl-5-isopropyl-*p*-phenetidine	4-OC_2H_5, 1-$NHCOCH_3$, 2-CH_3, 5-$CH(CH_3)_2$	Thymacetin		+		
N-Alkyl-4-Acetoxyacetanilides	1-$NRCOCH_3$, 4-$OCOCH_3$			++	+	
4-Ethoxyphenylurea	1-$NHCONH_2$, 4-OC_2H_5	Dulcin	±			−
Phenylurethan	—$NHCOOC_2H_5$	Euphorin	+			−
4-Hydroxyphenylurethan	1-$NHCOOC_2H_5$, 4-OH		++			−
4-Hydroxy-N-Acetyl-phenylurethan	1-$NCOOC_2H_5$, 4-OH (Ac on N)	Neurodin	+			−
4-Ethoxy-N-Acetyl-phenylurethan[68]	1-$NCOOC_2H_5$, 4-OC_2H_5 (Ac on N)	Thermodine	+	+		−
p-Acetamidophenyl-urethans[69]	1-$NHCOCH_3$, 4-NHCOOR		±			
2-Hydroxybenzal-N-methyl phenylhydrazone	$C_6H_5N(CH_3)$—N=CH-*o*-C_6H_4OH	Agathin	±	+		++
Levulinic Acid Phenylhydrazone	$C_6H_5NHN{=}C(CH_3)CH_2COOH$	Antithermin	+			++
Phenylsemicarbazide	$C_6H_5NHNHCONH_2$		+			+
3-Carbonamidophenylsemicarbazide	*m*-$H_2NCOC_6H_4NHNHCONH_2$	Cryogenin	++			−

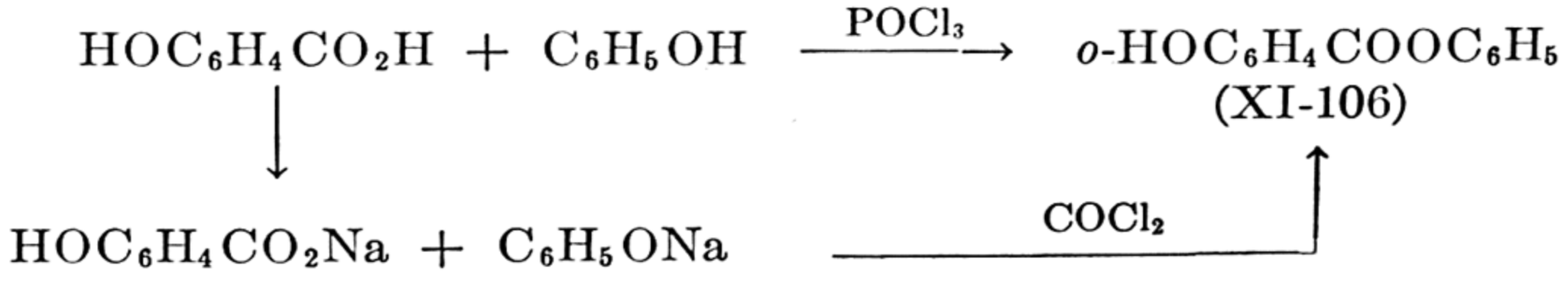
3. The Salicylates

The febrifuge and pain-relieving properties of salicylic acid and its salts have been utilized medicinally for over a century. In the form of its methyl ester (oil of wintergreen), salicylic acid has been used for the relief of muscular aches and neuralgias. The disadvantages of salicylic acid, particularly its toxic manifestations were recognized at an early stage, but since no other substitute was available, toxicity had to be accepted as an unavoidable side-action. However, its specific antipyretic action in rheumatic fever was recognized in 1876 by Stricker, and no other drug except ACTH and cortisone has become its rival in this condition.

The therapeutic mechanism of salicylic acid in rheumatic fever is still obscure. The disease is caused indirectly by a coccus infection, and has been represented as an allergic reaction to the bacterial toxins. The causative infection can be controlled with sulfonamide drugs or antibiotics, but prolonged treatment with salicylates is routine even after the actual disappearance of the bacteria.

The first synthetic ester of salicylic acid to be introduced into medicine was phenyl salicylate, (salol, *o*-$HOC_6H_4CO_2C_6H_5$) which Nencki[70] recommended as an antineuralgic and analgetic drug. He found that slow biological hydrolysis of the ester released into the organism the components, phenol and salicylic acid, in such small amounts that their toxic effects remained in the background, and only their antipyretic and bacteriostatic effects were noted (Nencki's salol principle).

Salol (XI-106) is prepared by heating salicylic acid and phenol with phosphorus oxychloride, or their sodium salts with phosgene according to the schemes:

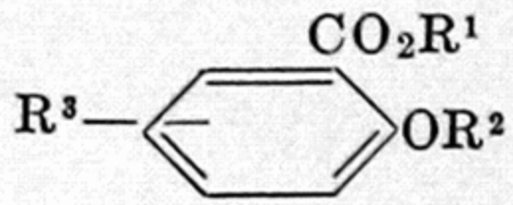


The drug has also been used as an intestinal disinfectant in diarrhea; it can be given in enterically coated pills.

Based on the salol principle, acetylsalicylic acid (XI-107) was prepared by Dreser[71] with the hope that this compound would be hydrolyzed slowly to salicylic acid. The compound was named aspirin and has been perhaps the most successful synthetic drug in the whole field of medicinal chemistry. It is used as a favorite antineuralgic and analgetic for lower types of pain as well as a mild sedative and excellent antipyretic. The preparation of

[70] Nencki, *Arch. exptl. Path. Pharmacol.*, **20,** 396 (1886); **36,** 400 (1895).
[71] Dreser, *Arch. ges. Physiol.*, **76,** 306 (1899).

TABLE X. THE SALICYLATES:

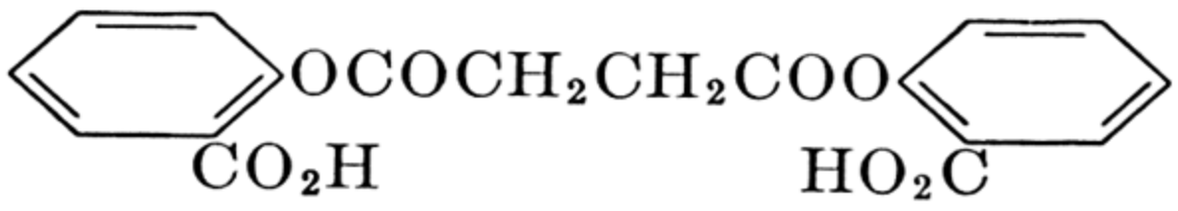


Compound	Synonym	R^1	R^2	R^3	Antipyresis	Analgesia	Depression	Toxicity
Salicylic Acid		H	H		++	++	+	++
Sodium Salicylate		Na	H		++	++	+	++
Acetylsalicylic Acid	Aspirin	H	$COCH_3$		++	++	+	±
Phenyl Salicylate	Salol	C_6H_5	H		+	+	+	±
Methyl Salicylate	Oil of Wintergreen	CH_3	H			+		++
Ethyl Salicylate	Sal Ethyl	C_2H_5	H			+		±
Amyl Salicylate	Ulmaren	C_5H_{11}	H			+		
Ethyl Salicylate Carbonate	Sal-Ethyl Carbonate	C_2H_5	$CO/_2$					
Ethylene Glycol Monosalicylate	Spirosal, Glysal	CH_2CH_2OH	H					
Trimethylacetyl Salicylate		H	$COC(CH_3)_3$			+		diuretic
Furoyl Salicylic Acid		H	CO-α-C_4H_3O		+	+		
4-Methyl-Acetylsalicylic Acid	Ervasin	H	$COCH_3$	4-CH_3	+	+		+
x-Allyl-Acetylsalicylic Acid		H	$COCH_3$	x-C_3H_5	++	++		
3-Benzyl-Acetylsalicylic Acid		H	$COCH_3$	3-$CH_2C_6H_5$	+	+		
Salicylsalicylic Acid	Diplosal, Salisal	H	$OCOC_6H_4COOH$-o					
Methyl Benzoylsalicylate	Benzosalin	CH_3	COC_6H_5					
Glycerol Monosalicylate	Glycosal	$CH_2CHOHCH_2OH$	H					
(2-Hydroxy-2-methyl-2-carbopropoxyacetyl) Salicylate		$CH_2C(CH_3)(OH)COOC_3H_7$	H					

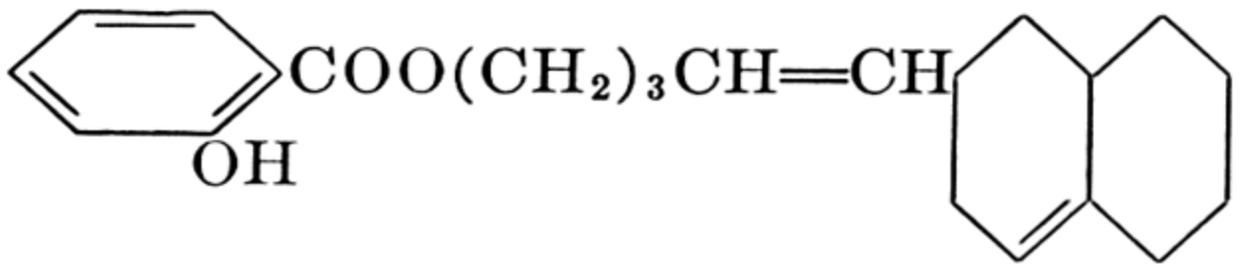
aspirin from salicylic acid and acetic anhydride, in the presence or absence of bases, is a classic and has not been changed much over the years.

$$o\text{-}HOC_6H_4COOH + (CH_3CO)_2O \rightarrow o\text{-}CH_3COOC_6H_4COOH + CH_3CO_2H$$
(XI-107)

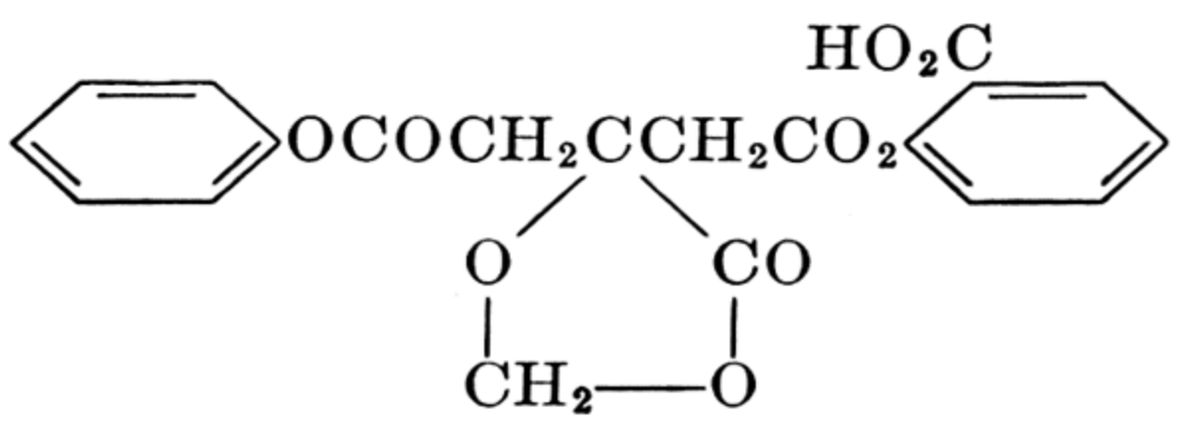
Some of the esters of salicylic acid lend themselves for topical application in neuralgias of the skin or the muscles under the skin. Oil of wintergreen, spirosal (so named for the spirea plant from which salicylic acid can be isolated), and other liquid derivatives of salicylic acid have found use in external application to swellings, rheumatic conditions, etc.



Diaspirin



Santalyl Salicylate (Santyl)



Methylene-citrylsalicylic Acid
(Novaspirin, Salicitrin)

Figure 7. Salicylates of More Complex Structure

More recently, salicylamide (o-$HOC_6H_4CONH_2$) has been introduced as an analgetic said to be as potent but less toxic than aspirin.

(2-Acetoxybenzyl) acetylsalicylate (o-$CH_3COOC_6H_4COOCH_2C_6H_4O$-$COCH_3$-$o$) is said to have the same analgetic effect as aspirin and five to ten times its duration of action.[72] Gentisic acid also controls symptoms of rheumatic fever.

The bacteriostatic and growth-inhibiting properties of salicylic acid and its derivatives with unobstructed phenolic hydroxyl groups are so much more pronounced than any of their other properties that large amounts of salicylic acid and certain salicylates have been used in the

[72] Martin and Urist, U. S. Pat. 2,474,005 (1949).

preservation of perishable foods by inhibiting their fermentation. The role of the salicylate ion in its microbiological behavior has been traced to an inhibition of certain essential metabolites, especially pantothenic acid. This antagonism will be discussed later in this book. If one keeps in mind that all the activities of the salicylates may be classified as depressive functions of cellular processes, both the growth-inhibiting and the antipyretic-antirheumatic properties of salicylic acid may well be based on similar mechanisms.

Substitution of salicylic acid by an amino group *para* to carboxyl has led to *p*-aminosalicylic acid (PAS) which has become one of the important antitubercular drugs of our day (see Chapter XXXVI).

4. Quinoline Derivatives

Certain quinoline derivatives are strongly antipyretic as well as antiseptic. Many of them act as central nervous system depressants and exhibit considerable toxicity. The activities of quinoline and its simple alkyl derivatives as well as of isoquinoline are progressively weakened by alkyl substitution but the position of the alkyl group does not seem to be particularly significant.

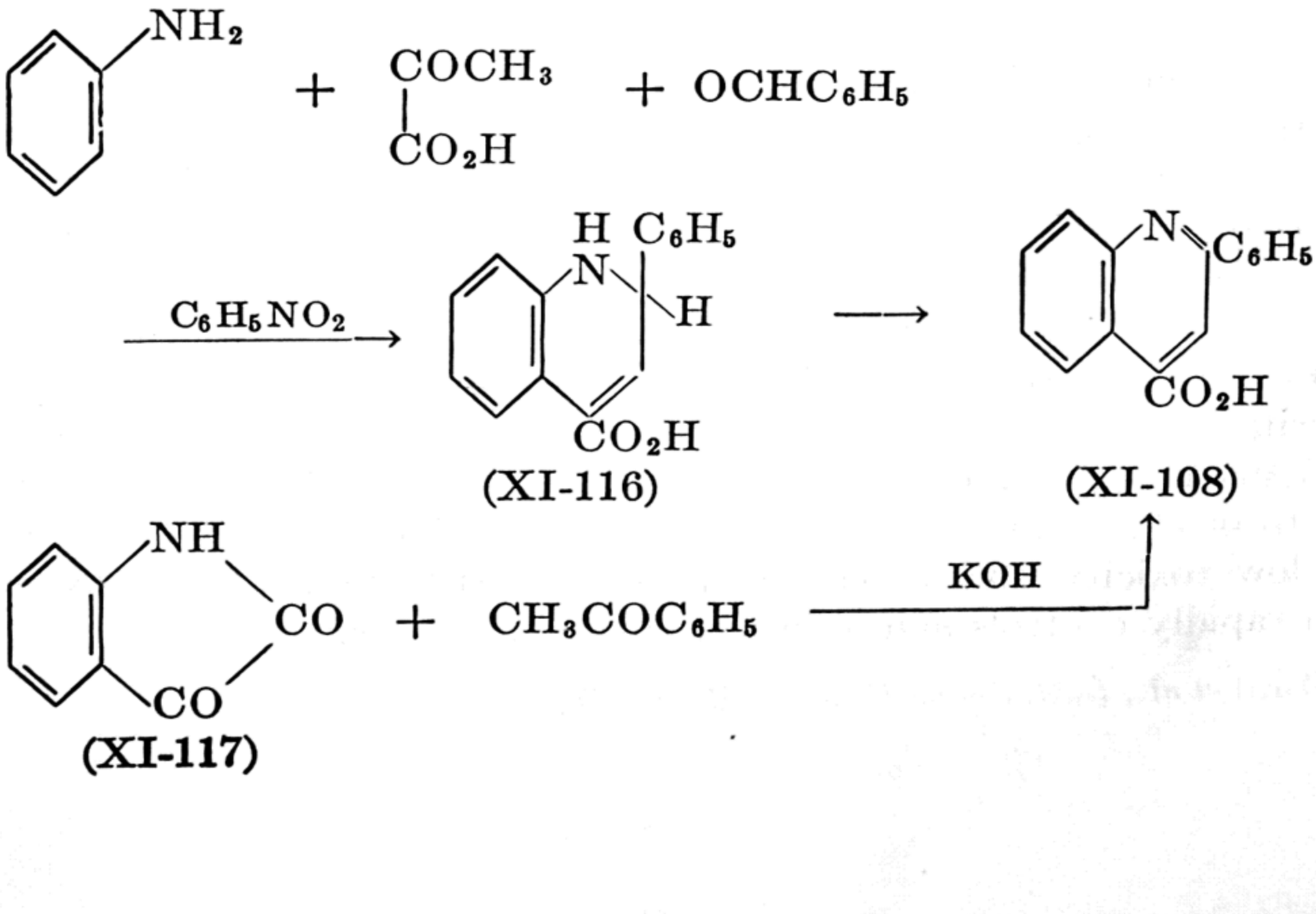
As might be expected, quinoline derivatives containing groups similar to those found in acetophenetidine have antineuralgic and antipyretic activity. Likewise, alkoxyquinolines lower fever temperatures but are mainly antiseptic. The more interesting alkoxyquinolines of the series, however, do not cause antipyresis in spite of their high antimalarial activity. 5-Benzamido-8-ethoxyquinoline was called analgen because of its pronounced antipyretic analgetic activity, but it is too insoluble and too erratic in its action to be of any use. Nupercaine is a widely used local anesthetic (see Chapter VIII); here the centrally depressant properties are mostly covered and local anesthetic properties have been bared.

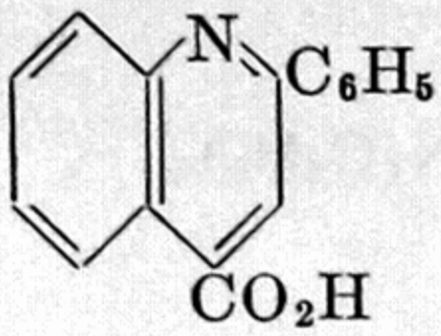
2-Phenylcinchoninic acid (cinchophen, Atophan, XI-108) has been used for the treatment of gout. It is said to promote the secretion of uric acid from the tissues of podagric individuals; in addition, it also exhibits a distinctive analgetic and antipyretic action similar in degree to that of the salicylates. Although it is five times more toxic than cinchoninic acid (LD, 1 g./kg.) it has been used widely for the relief of pain. Table XI and Figure 8 show structural variations of cinchophen designed to produce a non-irritating, less toxic compound with a greater central depressant action than the parent compound. Some of the derivatives have been claimed to produce long-lasting analgesia. Hexophan (XI-118) is said to have a low toxicity and to cause almost no irritation. 3-Hydroxycinchophen rapidly controls symptoms of rheumatic fever.[72a]

[72a] Blanchard *et al.*, *Bull. Johns Hopkins Hosp.*, **87,** 50 (1950).

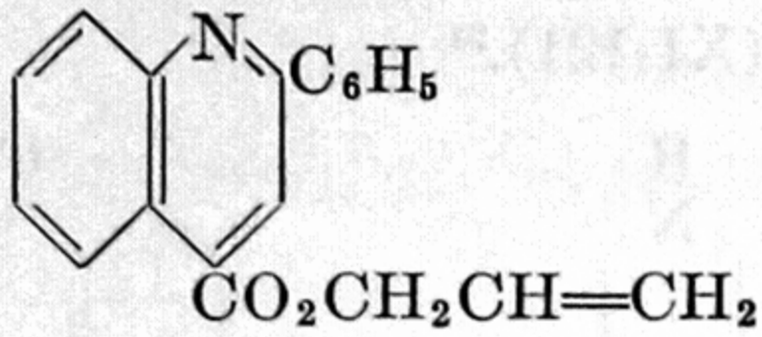
TABLE XI. ANALGETIC-ANTIPYRETIC DERIVATIVES OF QUINOLINE

Derivative of Quinoline (Synonym)	Antipyresis	Analgesia	Other Actions	Toxicity
5-Acetamido-6-ethoxy-	+	+		
5-Benzamido-6-ethoxy-	+	+		
2-Methyl-4-phenyl-	±		Central excitation	
2-Methyl-4-phenyl-6-methoxy-	+		Protozoicidal	
6-Methoxy-8-amino-	+		dto.	
5-Benzamido-8-ethoxy- (Analgen)	+		Antiseptic. Stimulates, then depresses centrally	
(Cinchophen, Atophan) (XI-108)	+	+		+
Hexamethylenetetramine Salt of Cinchophen		++		
Allyl 2-phenylcinchoninate (XI-109) (Atoquinol)	++	+		−
Ethyl 2-phenyl-6-methylcinchoninate (Neocinchophen, Tolysin) (XI-110)	+	+		−
(Synthallin) (XI-111)		+		
2-(2-Furyl) cinchoninic acid (XI-112)		+		−
2-(2-Thienyl) cinchoninic acid (XI-113)		+	Antiphlogistic	+
3-Aminocarbostyril (XI-114)	+		Forms methemoglobin	++
1-Aminocarbostyril (XI-115)	+			++
1-Ethyl-8-hydroxy-1,2,3,4-tetrahydroquinoline (Kairine)	+		Forms methemoglobin	+
6-Methoxy-1,2,3,4-tetrahydroquinoline (Thalline)	+			
	+			
	+++			

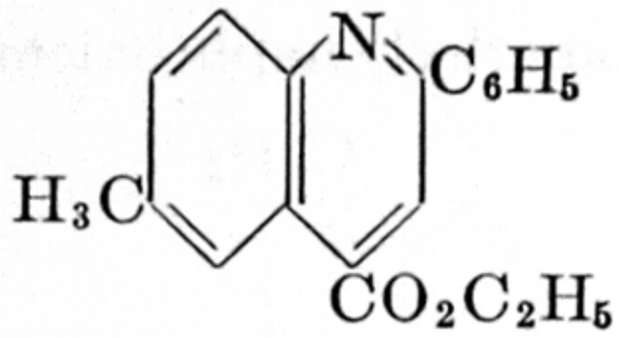




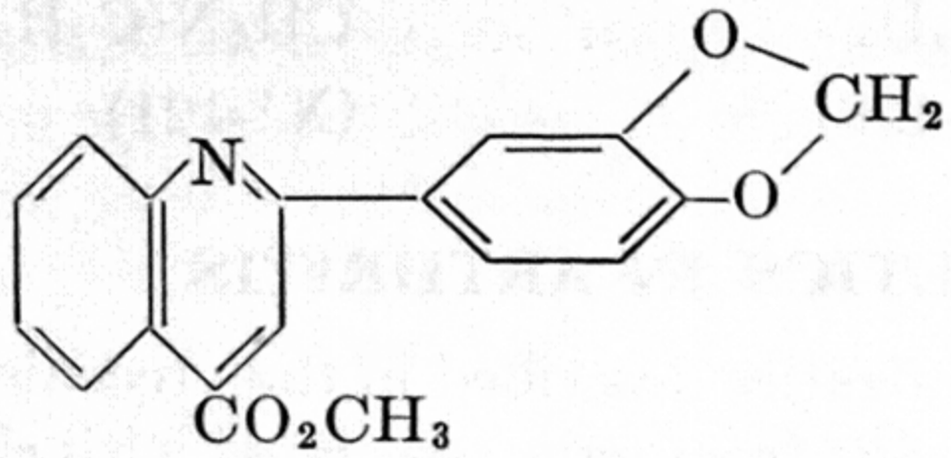
(XI-108)



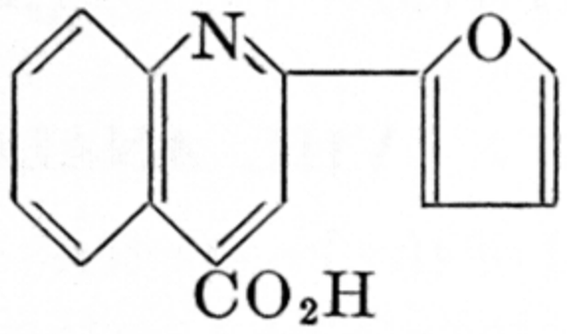
(XI-109)



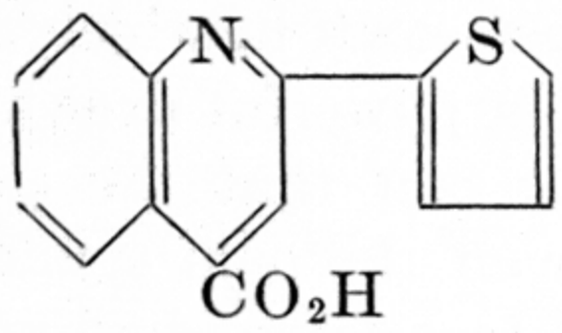
(XI-110)



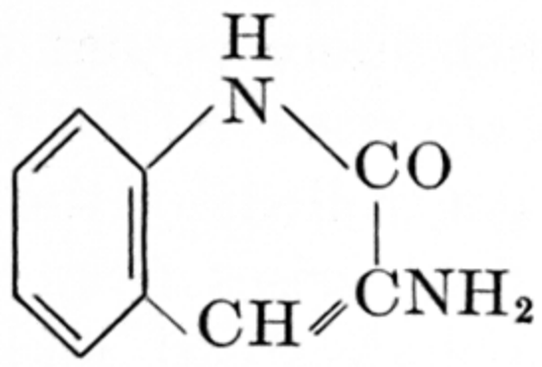
(XI-111)



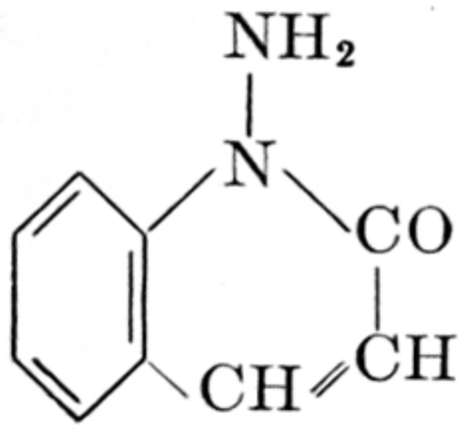
(XI-112)



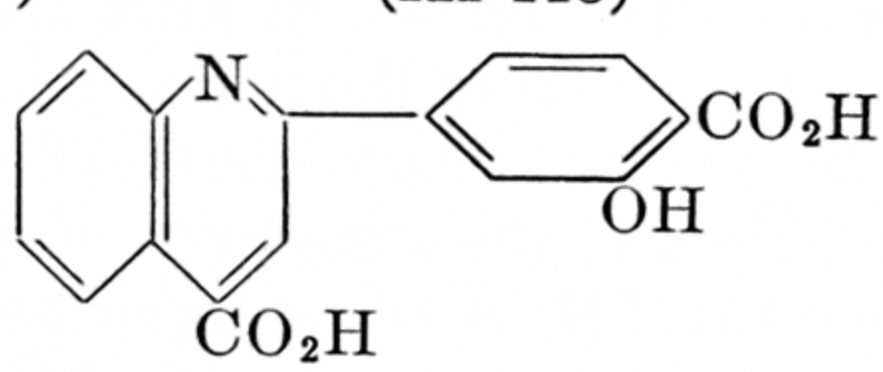
(XI-113)



(XI-114)



(XI-115)



Hexophan (XI-118)

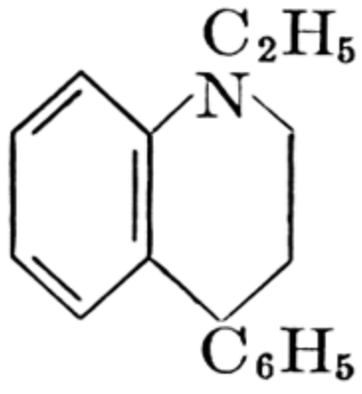
Figure 8. Formulas of Some Analgetic Quinoline Derivatives

Cinchophen has been synthesized by many methods. For example, its 1,2-dihydro derivative is formed when aniline, benzaldehyde and pyruvic acid are condensed. The dihydro compound (XI-116) is oxidized readily to cinchophen (XI-108). Another route utilizes the alkaline condensation of isatin (XI-117) and acetophenone (see page 204).

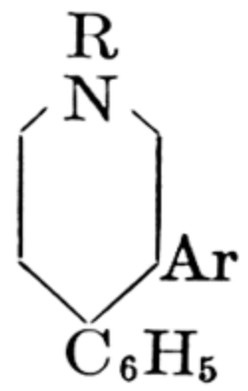
Reversal of the phenyl and carboxyl groups as shown in 4-phenylquinoline-2-carboxylic acid leads to an ineffective compound. The only advantage of neocinchophen (XI-110) is its indifferent taste as compared with the exceedingly bitter taste of cinchophen.

1-Ethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (XI-119) shows analgetic and antispasmodic effects. It is also possible to transfer the condensed benzene ring to a single-bonded position without loss of activity as shown in several 1-alkyl-3-aryl-4-phenylpiperidine derivatives (XI-120) which possess similar properties. During the experiments with these compounds, marked analgetic activity was detected even in 1,4-bis-(diethyl-

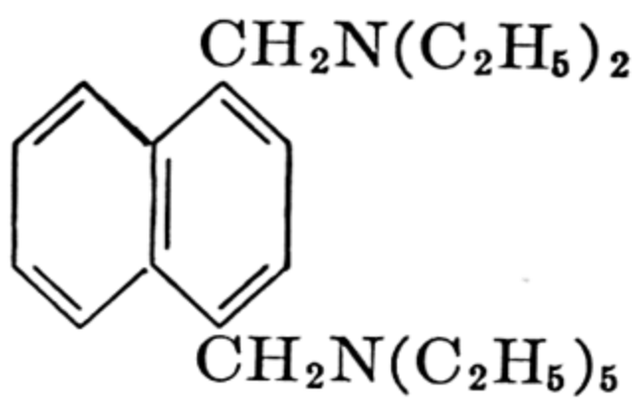
aminomethyl)-naphthalene (XI-121).[73]



(XI-119)



(XI-120)



(XI-121)

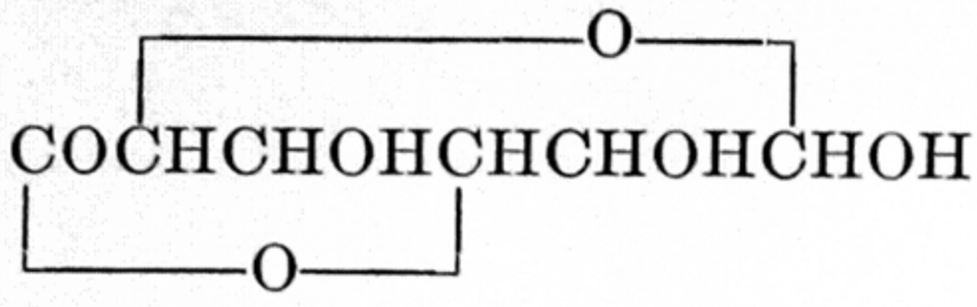
VIII. ANALGETICS IN ARTHRITIS

Several of the less potent analgetics described in the preceding sections of this Chapter afford a certain relief from pain associated with rheumatoid arthritis and its subdivisions. The salicylates, Acetophenetidine and its analogs, and the drugs of the cinchophen series have been used with varying degrees of success. The much more potent opiates as well as methadon and other potent synthetics are reserved for those cases in which arthritis pain exceeds the threshold controlled by the less powerful drugs.

The confusion in this field arises from the fact that the causative mechanism of arthritis is not understood, and even the pain syndrome of the disease is not well defined. During the last few years, the hypothesis has been proposed that arthritis is a deficiency disease caused by an impaired function of the hormones of the adrenal cortex. This view is based on the ability of certain steroid hormones such as cortisone, to relieve both the pain and the symptoms of the disease. The adrenocorticotropic hormone (ACTH) of the anterior lobe of the pituitary gland, which stimulates secretion of cortisone by the adrenal cortex, brings about similar effects in large doses. The hormones involved in this field are being discussed in Chapter XXIX.

Arthritis is a disease in which the cement substance of bone and cartilage, collagen, is destroyed.[74] It has been suggested that this condition may be caused by a deficiency of glucuronic acid which is a normal biological oxidation product of glucose and is used by the body for biological conjugation of toxic products prior to their excretion. Experiments with the lactone of glucuronic acid (XI-122) showed that early cases of osteo-arthritis responded well to treatment with this substance; pain decreased, and the swelling of the joints receded. In rheumatoid arthritis, the results were less effective, but excellent response to glucuronic acid treatment was obtained in sciatica.

[73] Badger, Cook, Donald, Graham, and Walker, *Nature*, **162,** 21 (1948).
[74] Peterman, quoted in *Chem. Eng. News*, **28,** 45 (1950).



(XI-122)

To these structurally widely divergent substances which barely influence arthritic conditions by the same biological mechanism, several others have been added in scattered observations. One of these concerns gold salts. Gold-sodium thiomalate (Myochrysine, $NaOOCCH(SAu)CH_2$-$COONa$) has been used both for rheumatoid arthritis and for the local treatment of the disease, lupus erythematosus. Similar copper compounds, e.g., cuproallylthiourea, $HN{=}C(SCu)NHCH_2CH{=}CH_2$, have also been recommended. The latter is supposed to be effective in neuralgias.

Another unexpected antiarthritis drug was discovered in Tibione, the thiosemicarbazone of *p*-formylacetanilide,

$$p\text{-}CH_3CONHC_6H_4CH{=}NNHCSNH_2.$$

This compound has been studied extensively as an antitubercular agent[75] but its antirheumatic properties were discovered only recently.

Heilmeyer[76] based his reasoning on certain modern concepts of rheumatic disease, which involves the theory that there is a chronic sensitization in rheumatism against defensive reactions which, influenced by the natural constitution of the individual, become independent of the exciting organism. As a consequence, all possible bacterial, chemical or physiological stimuli may continue to maintain the state of the disease. Such states are called hyperergic.

Tibione seems to act both on the tubercle bacillus directly like an antibiotic, and also on some unspecific reaction of the bacillus in the blood stream, and on the defense mechanism of the host. Reappearance of a deteriorated blood picture when treatment is stopped, and a decrease of the copper content of the serum of tuberculous individuals have been observed in the study of Tibione. Similar effects are known to take place in chronic rheumatic diseases, and hence Tibione was tested in polyarthritis. The results of these tests were very encouraging.

Relief from pain arising in the joints during acute exacerbations of rheumatoid arthritis has also been obtained with tetraethylammonium bromide (Chapters XXI and XXII). The duration of action of this drug was considerable.[77]

[75] Domagk, *Schweiz. Z. Path. Bakt.*, **12,** 575 (1949).
[76] Heilmeyer, *Deut. med. Wochsch.*, **74,** 161 (1949).
[77] Howell, quoted in *Chem. Eng. News*, **28,** 1395 (1950).

CHAPTER XII

Analeptics

I. INTRODUCTION

The literal definition of an analeptic, based on its etymological derivation, is that of an agent which restores health.[1] This concept is too broad to provide a valuable classification for the purposes of this volume. Clark[2] has followed the more classical lead of the older medicinal literature by applying the term analeptic to drugs with central nervous excitatory action. Other pharmacologists prefer to lean towards a classification based on the therapeutic use of the drugs rather than on the pharmacological mechanism of their action. Thus, Goodman and Gilman[3] assign the name analeptic to the restricted group of drugs which arouse the animal organism from a state of narcosis. The obvious objection to this interpretation is the lack of understanding of narcosis. Morphine and many of its derivatives are classical examples of narcotics, and yet analeptics cannot be used without grave danger in morphine poisoning because the particular depression and fatigue of the respiratory centers produced by overdoses of morphine are aggravated by the depression following large doses of at least certain typical analeptic drugs.[4] The most suitable definition of an analeptic is perhaps that of a drug which can stimulate the vital medullary centers when they are in a depressed state.[1] The depression may be brought about by overdoses of certain drugs, especially by barbiturate poisoning. It may also be due to certain as yet not clearly understood pathological causes, such as narcolepsy, and psychic depressions.

Cannon proposed the term homeostasis for the normal equilibrium of balancing physiological effects of glandular secretion, nervous impulses and other conditions which we identify with normal health. Any deviation from this equilibrium will provoke reflexes which tend to restore the state of equilibrium. The most adequate description of homeostasis is

[1] Hazleton, *J. Am. Pharm. Assoc.*, **33,** 65 (1944).
[2] Clark, *Applied Pharmacology*. Blakiston, Philadelphia, 1940.
[3] Goodman and Gilman, *The Pharmacological Basis of Therapeutics*. Saunders, Philadelphia, 1941.
[4] Hazleton and Koppanyi, *Anesthesiology*, **2,** 427 (1941). Maloney, *Quart. J. Exptl. Physiol.*, **25,** 155 (1935). Barlow, *J. Lab. Clin. Med.*, **23,** 601 (1938). Dille and Hazleton, *J. Pharmacol. Exptl. Therap.*, **67,** 276 (1939).

the maintenance of a constant and optimal concentration of available oxygen, glucose, carbon dioxide, hydrogen ions, coenzymes, apoenzymes and other essential nutrients and environmental factors of the central nervous system.

Failure of homeostasis results from disturbances of any of these factors, and the mission of analeptics is to compensate for these irregularities. Changes in the composition of arterial blood carrying oxygen and glucose to the brain lead to respiratory depression or cessation. Any circulatory derangement, characterized by low blood pressure in the whole system or by purely local disturbance (cerebral arterial spasm, embolism or rupture) leads to similar symptoms. Vitamin deficiencies, acidosis, ketosis, uremia, drug poisoning, and other enzymatic disturbances of the central nervous system also cause acute central nervous depression. Analeptic drugs have to counteract any or all of these conditions, and an overall judgment of their mechanism of action is therefore very difficult to achieve.[5]

Since analeptics are most effective when they arouse the organism from narcotic depression, the mechanism of action of narcotics and analeptics must be closely related. The most widely accepted explanation of the pharmacological mechanism of analeptics is one of physiological antagonism to depressant drugs: the stimulatory effect of analeptics on the central nervous system overbalances the narcotic effect of barbiturate poisoning. It has even been shown that a mixture of convulsive amounts of a hypnotic and an analeptic drug can be injected without producing a marked effect in either direction.

A biochemical explanation of the action of analeptics must thus be based on an understanding of the mechanism of hypnotics, and the latter is still obscure. Since the narcotics appear to inhibit dehydrogenases in carbohydrate metabolism, analeptics must cancel this inhibition. There is no evidence for the belief that analeptics promote the action of oxygen-transmitting enzyme systems such as cytochrome C; the stimulatory effect of analeptics on respiration had led to this assumption.

Most students of analeptics agree that picrotoxin is the most potent central nervous system stimulatory drug. It is followed, in descending order, by Metrazol and nikethamide. Three other active compounds, the alkaloids strychnine, atropine, and caffeine, are no longer used as extensively by the medical profession.

Any compound which improves the metabolic effectiveness of the central nervous system will, of course, contribute to its normal functioning. The biocatalysts of the vitamin B complex, as well as actual metabolite members of the carbohydrate cycles, have mildly analeptic properties.

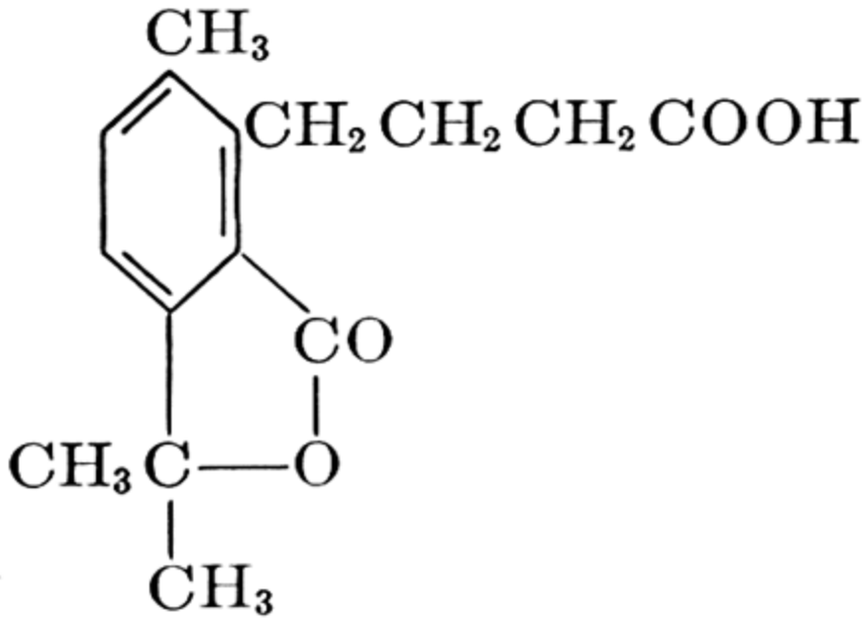
[5] Eckenhoff, Schmidt, Dripps, and Kety, *J. Am. Med. Assoc.*, **139,** 780 (1949).

Addition of succinic, pyruvic or fumaric acid to the diet has proved valuable in experiments with centrally depressed animals. Carbon dioxide is the stimulant of choice in many cases of respiratory depression. It acts by a physiological mechanism differing from other drugs and metabolites discussed here.

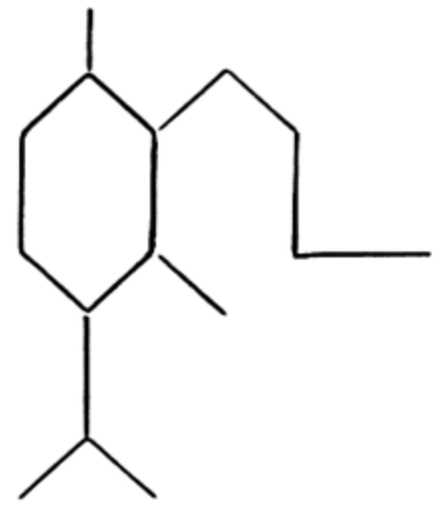
II. PICROTOXIN

Picrotoxin is an equimolecular compound of two dilactones, picrotoxinin ($C_{15}H_{16}O_6$) and picrotin ($C_{15}H_{18}O_7$). It constitutes the bitter principle of the berries of certain *cocculus* shrubs, for example, *Anamirta cocculus* or *Cocculus indicus*. Picrotoxin is the most powerful analeptic agent used in therapy, and a formidable pharmacological literature has accumulated on its properties. It is used exclusively for the treatment of barbiturate poisoning and intoxication by other central nervous depressants.

The chemistry of the two constituents of picrotoxin has not yet been properly defined. Hydrolysis of either picrotoxinin or picrotin gives the same products, picrotic acid (XII-1) and a ketone, $C_{14}H_{16}O_3$, which points to a common carbon skeleton (XII-2) for both lactones.[6] This relation has been confirmed by a number of reactions.[7] It has also been pointed



(XII-1)



(XII-2)

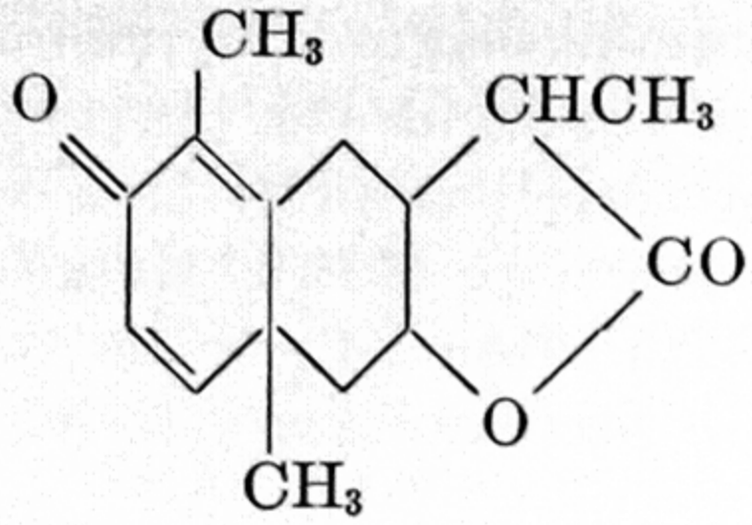
out that the proposed carbon skeleton links the constituents of picrotoxin to the sesquiterpene group, and establishes their relation to other stimulatory lactones, such as santonin (XII-3).[8]

It is not possible to pin a certain pharmacological activity on a given structural unit. This chapter dealing with analeptics of so many different types is ample proof for this postulate. Nevertheless, one cannot escape

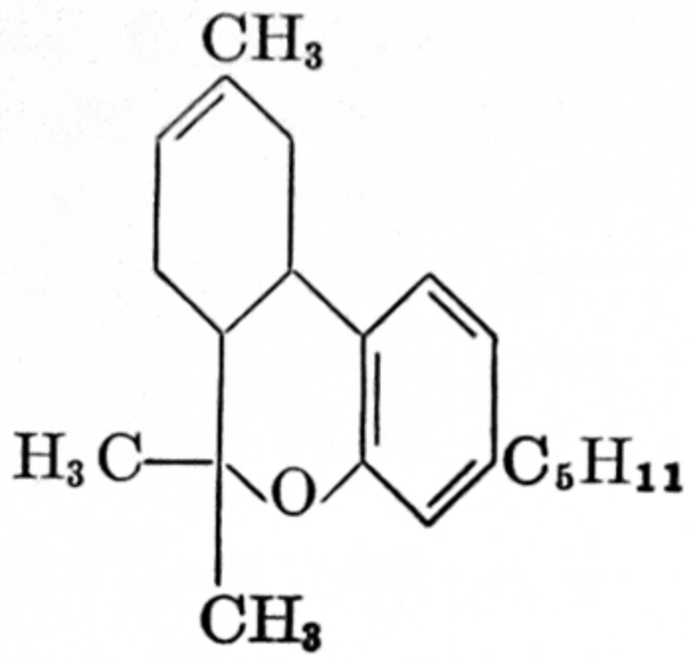
[6] Angelico, *Gazz. chim. ital.*, **41,** 337 (1911); **42,** 540 (1912). Mercer, Robertson, and Cahn, *J. Chem. Soc.*, 997 (1935).

[7] Harland and Robertson, *J. Chem. Soc.*, 937 (1939). O'Donnell, Robertson, and Harland, *ibid.*, 1261 (1939). Kariyone and Sato, *ibid.*, 50 (1943). Soater, *ibid.*, **143** (1943).

[8] Clemo, Haworth, and Walton, *ibid.*, 2368 (1929).



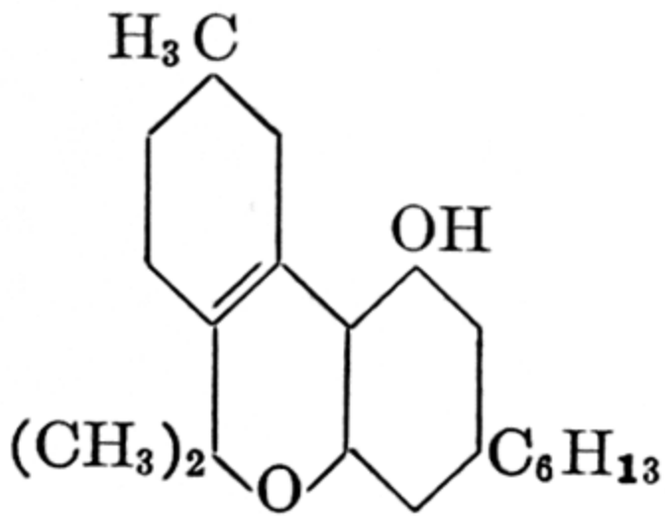
(XII-3)



(XII-4)

the observation that the lactone group is present in various stimulatory drugs, from the cardiotonic digitalis aglycones to santonin and picrotoxin.

There exists also a generic relation between oxidation products of picrotoxinin and picrotin, and of tetrahydrocannabinol (XII-4), the pharmacologically active ingredient of *Cannabis indica* resin (hashish, marihuana) which acts as a euphoric stimulant. A similar compound, 1-hydroxy-3-*n*-hexyl-6,6,9-trimethyl-7,8,9,10-tetrahydrodibenzopyran (XII-4a) has been introduced under the names of Synhexyl, Parahexyl or Pyrahexyl. Its euphoric effect resembles that of cannabis; it is said to reverse thalamic dysfunction, causing neurotic depressions. In spite of this, it has been tried in the treatment of depressive patients and drug addicts.



(XII-4a)

III. METRAZOL

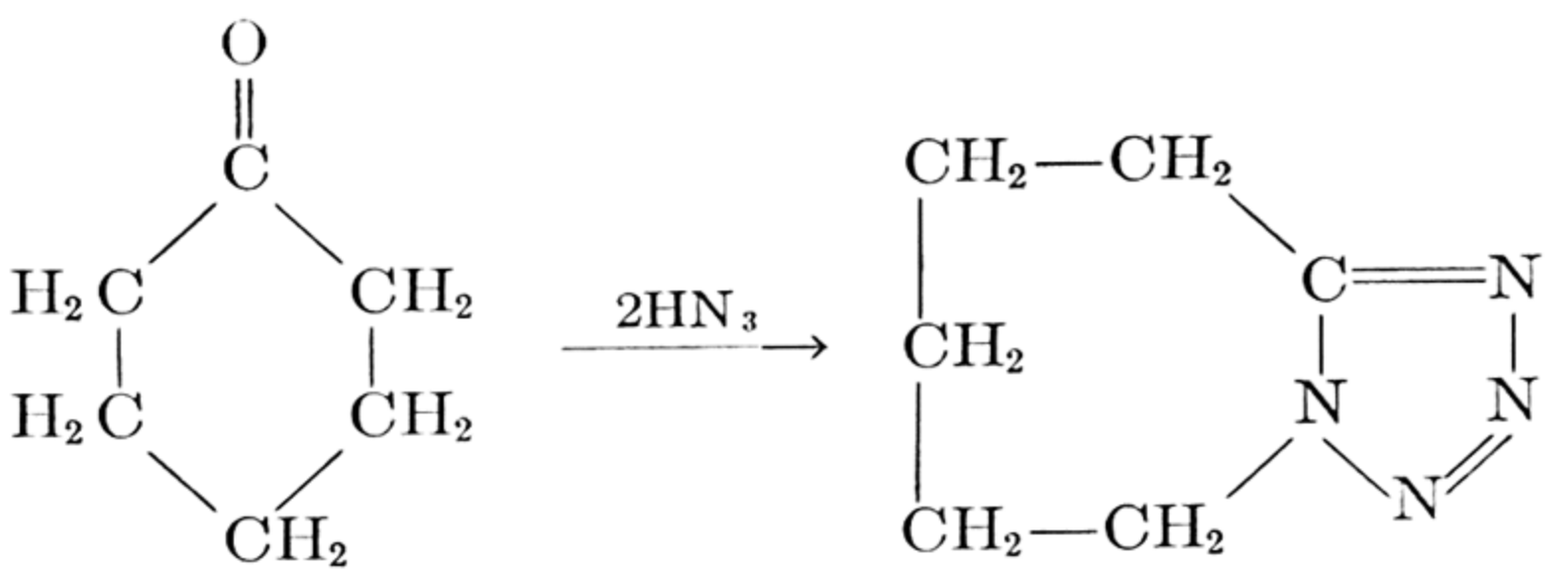
Metrazol, previously called cardiazole in Europe, is the name of 4,5-pentamethylenetetrazole (XII-5) whose structure contains the unusual combination of two condensed five- and seven-membered heterocyclic rings. There are many statements in the pharmacological literature that its formula was conceived in an imitation of that of camphor, "the six carbon ketone of camphor having been condensed with a nitrogenous chain in the way of a hydrazone", but this idea completely lacks chemical background. Metrazol stands by itself as a useful drug in the field of analeptics.

Metrazol is one of the most rapidly acting, although not the most effective analeptic. Its ability to arouse individuals from barbiturate-

induced sleep has been found useful in terminating mild hypnotic intoxication since only small doses of Metrazol are needed for this purpose. Larger doses of the drug cause convulsions. Metrazol is rapidly metabolized and destroyed in the liver and its action is therefore of brief duration. This quick disappearance from the system aids further a favorable therapeutic index in making a small analeptic dose of Metrazol a relatively safe therapeutic tool.

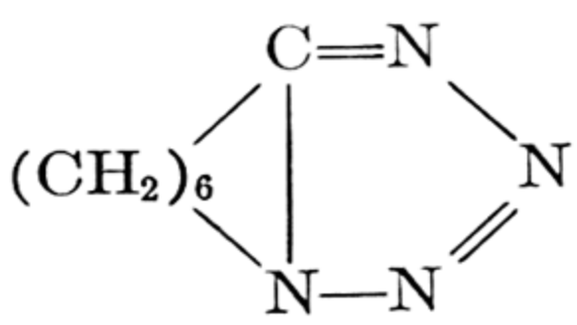
Larger, near-toxic doses of Metrazol produce severe convulsions, and these are being used in the successful shock treatment of schizophrenia and other mental disorders. The high incidence of fractures of thoracic vertebrae caused by Metrazol convulsions makes it imperative to paralyze the muscles of the back, etc. by simultaneous injection of curare or curariform drugs. Metrazol has implemented insulin in producing convulsions in psychiatric procedure, and has been replaced, in turn, by electroshock in many instances.

Metrazol is synthesized from cyclohexanone and hydrazoic acid.[9]

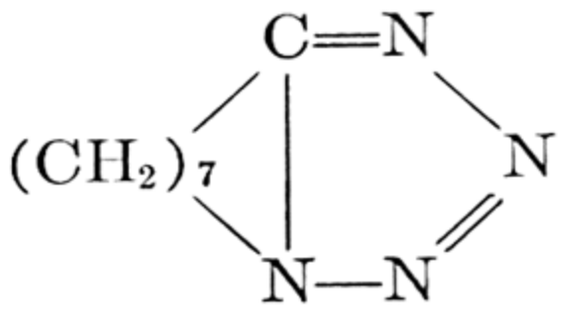


(XII-5)

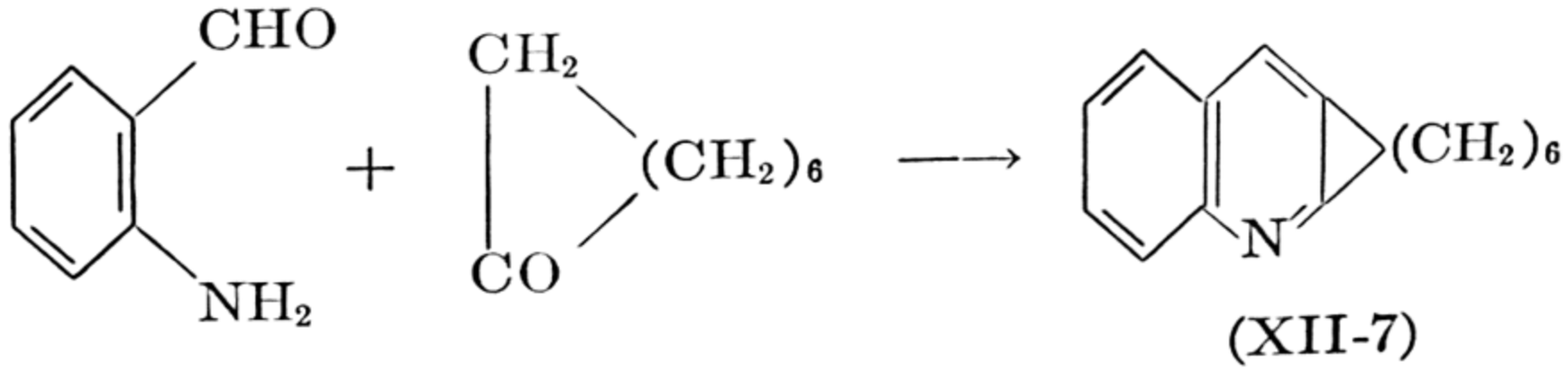
Many other tetrazoles derived from cyclic ketones have been prepared but none of them has attained analeptic application. Starting from cyclo-



(XII-6a)



(XII-6b)



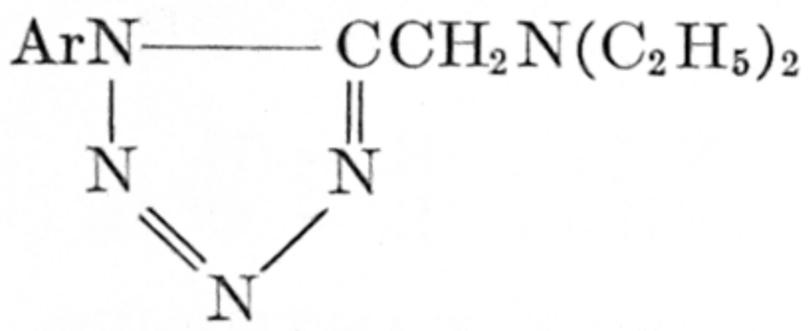
(XII-7)

[9] Schmidt, U. S. Pat. 1,599,493 (1926); *Ber.*, **57,** 704 (1924).

heptanone and cyclooctanone and hydrazoic acid, the tetrazole derivatives (XII-6a and 6b) were prepared.[10] They behaved like Metrazol but did not show any advantage over this drug. It is interesting that 2,3-cyclohexamethylenequinoline (XII-9), prepared from anthranilaldehyde and cyclooctanone, exhibited a strong action on the heart.

The tetrazole derivatives prepared from camphor, and from a mixture of α and β-thujone, respectively, under the influence of hydrazoic acid have analeptic activity and are said to be free from paralyzing properties.[11]

Several basically substituted phenyl and naphthyl tetrazoles (XII-8) have been recommended as sedatives and anesthetics.[11a]



(XII-8)

IV. STRYCHNINE

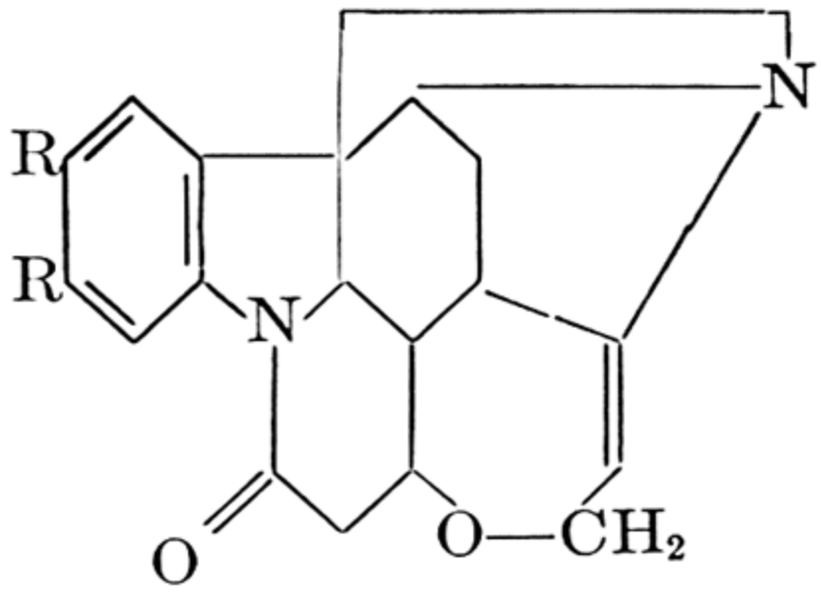
Strychnine (XII-9) is the principal alkaloid found in the poisonous nuts of the tropical tree, *Strychnos nux vomica*, and is the cause of the toxic properties of these nuts. It is accompanied by several minor alkaloids, of which brucine and vomicine should be mentioned. Brucine (XII-10) is dimethoxystrychnine and has no value even as a poison for rats and other animal pests[12] for which strychnine is still widely used. Vomicine has found no particular use; its chemistry has been studied by Wieland.

The structure of strychnine has offered some of the most obstinate hurdles to recent deductive analysis. It has been elucidated by studies comprising almost two hundred papers by Leuchs, by Robinson and finally by Woodward.[13] There is nothing in its formula to explain its physiological properties in comparison with that of much less complicated analeptics. It is even harder to explain the failure of brucine as a therapeutic agent on the basis of the minor substitutions of the strychnine molecule.

Pharmacologically, strychnine is diametrically opposed to the action of the barbiturates. It is sometimes possible to use strychnine in arousing a patient from barbiturate sleep but ordinarily the alkaloid exerts this action only in toxic doses. Vice-versa, strychnine poisoning and convulsions can be overcome by short-acting barbiturates. The only reliable

[10] Ruzicka, Goldberg, and Hürbin, *Helv. Chim. Acta*, **16,** 1335 (1933).
[11] Schmidt, U. S. Pat. 2,029,799 (1936).
[11a] Harvill and Herbst, U. S. Pat. 2,470,085 (1949).
[12] Henry, *The Plant Alkaloids*. Blakiston, Philadelphia, 1949, p. 561 ff.
[13] Woodward and Brehm, *J. Am. Chem. Soc.*, **70,** 2107 (1948).

actions of small non-toxic doses of strychnine are its increase of the tone of skeletal muscle following general anesthesia, and its stimulation of respiration in deep centrally depressed states.



(XII-9), R = H
(XII-10), R = OCH_3

V. THE XANTHINES

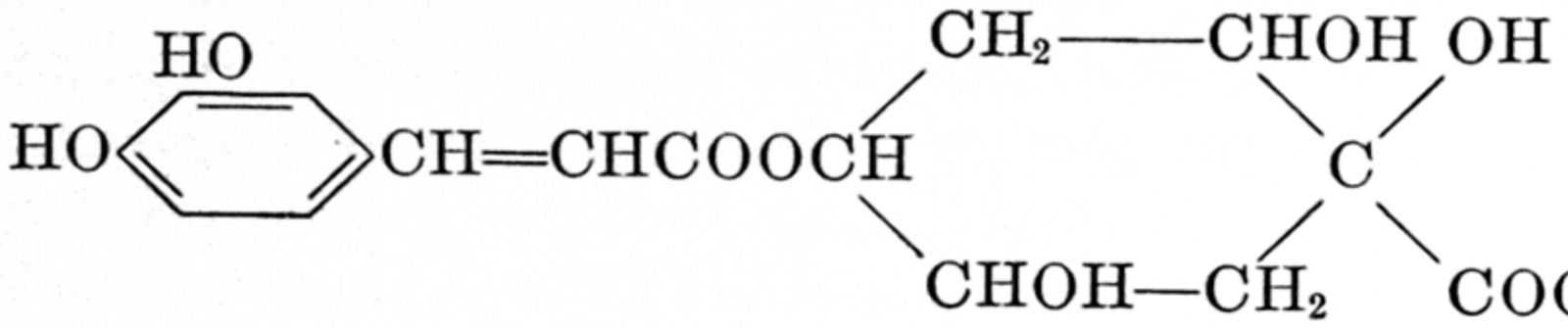
Only two xanthine derivatives are employed as analeptics, namely, caffeine and theophylline, and even the more potent of the two, caffeine, is used only to a limited extent. Caffeine is still given intramuscularly in cases of morphine poisoning. There are several side-effects of both caffeine and theophylline which can be exploited therapeutically. The diuretic action of these compounds will be discussed in Chapter XV. They also produce coronary vasodilation and have therefore been used in angina pectoris. Theophylline, combined with ethylenediamine (see Chapter XV) is widely used in bronchial asthma, and in certain heart diseases (paroxysmal nocturnal dyspnea due to left ventricular insufficiency). Perhaps the best known use of caffeine is in headaches but here it is usually taken in the form of coffee rather than as the pure drug.

Caffeine (XII-11) occurs in the seeds of *Coffea arabica* from which coffee is made, as well as in tea (1–4.8%), the dried leaves of *Thea sinensis*. This product also contains theophylline. Other sources of caffeine include maté, which is widely drunk in South America and contains 1.25–2% of the alkaloid. The African kola nut contains 2.7–3.6% of caffeine, and an even larger percentage (up to 5%) is found in the South American guarana paste. In all these materials, caffeine occurs in the free state or as the potassium chlorogenate. Chlorogenic acid (XII-12) is a depside of caffeic acid and quinic acid.

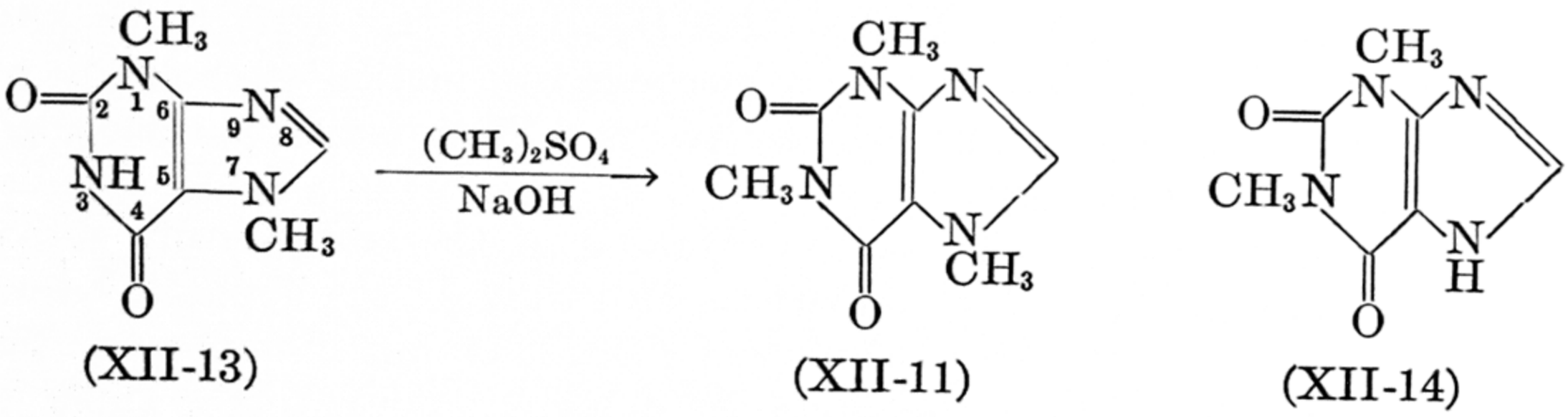
Theobromine (XII-13) is the main alkaloid of the beans of *Theobroma cacao*. It is barely stimulatory on the central nervous system but has considerable diuretic activity.

Theophylline (XII-14) occurs in small amounts in tea but is manufactured entirely synthetically.

Coffee is the most common source of caffeine in its native form. Coffee contains approximately 1.29% of caffeine, one cup of coffee corresponding to 100–150 mg. of the alkaloid. On the basis of a recent estimate, the American people consume about five to six million kilograms of caffeine per year in coffee alone. The amount consumed in tea must be added to these figures. The regular and continued ingestion of caffeine has raised the question as to whether habituation to the drug is a menace to health. It is most probable—although not certain—that mild habituation to caffeine occurs in many individuals, but severe untoward effects have not been observed as a result of this habit.



(XII-12)



(XII-13) (XII-11) (XII-14)

The chemistry of purine derivatives has been reviewed several times in recent years,[14] and only a bare outline of the medicinally important xanthine derivatives shall be given here.

Caffeine is 1,3,7-trimethylxanthine, theobromine is the 3,7-dimethyl derivative, and theophylline 1,3-dimethylxanthine. All three substances can be obtained synthetically by the method of Traube[15] but caffeine is usually manufactured by special methods.

A certain amount of caffeine is still obtained by extraction of tea wastes with boiling water, precipitation of tannins with magnesium hydroxide and evaporation of the filtrate. The manufacturers of caffeine-free coffee obtain the alkaloid as a by-product. Most commonly, caffeine is now prepared by methylation of theobromine with methyl sulfate in alkaline medium.[16] Theobromine is an otherwise useless by-product obtained from the hulls of cacao beans during the manufacture of cacao and of chocolate.

[14] Johnson, in Gilman, *Organic Chemistry*, Vol. II. Wiley, New York, 1938, p. 948. Lythgoe, *Quart. Revs. London*, **3,** 181 (1949).
[15] Traube, *Ber.*, **33,** 1371, 3035 (1900).
[16] Biltz and Damm, *Ann.*, **413,** 190 (1916).

Much of the caffeine prepared in this manner is added to "soft drinks" which owe their mildly stimulating action to this drug.

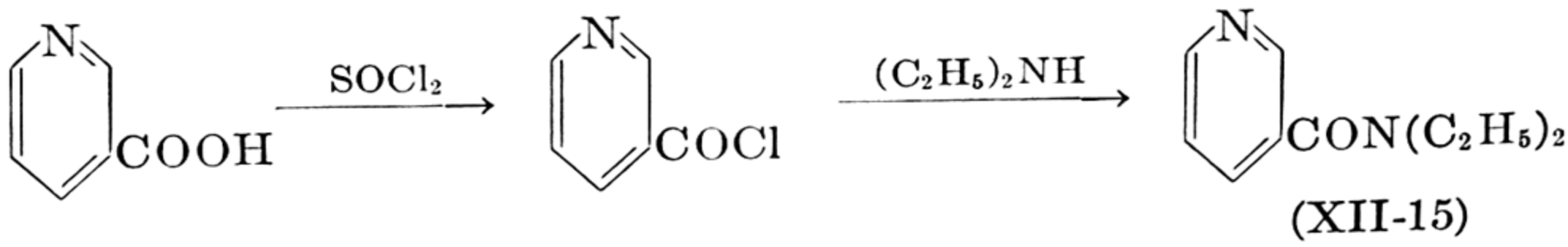
The chemistry and manufacture of theophylline may be studied in connection with its use as a diuretic (Chapter XV).

Considering the fact that caffeine is much more stimulatory than its lower dimethyl homologs, theobromine and theophylline, and that xanthine and 1, 9-dimethylxanthine are inactive, the metabolic fate of caffeine in the organism is noteworthy. Caffeine is demethylated biologically to some of these less analeptic compounds, in man primarily to theophylline, in the dog to theophylline, theobromine, paraxanthine and 3-methylxanthine.[17] It has been suggested that the liberated methyl radicals may be responsible for the action of caffeine[18] but it is more likely that the structure of the whole molecule, plus its rate of enzymatic degradation contribute to the observed effect. If one would lend credence to the hypothesis that the liberation of methyl groups accounts for the analeptic activity of caffeine, one could expect choline ($HOCH_2CH_2N(CH_3)_3 \cdot OH$) to be pronouncedly analeptic since the main biochemical function of choline is to supply methyl groups for transmethylations. There is no pharmacological basis for this assumption.

A superficial inspection of the formulas of the analeptically active xanthine derivatives, and a comparison with those of the hypnotic barbiturates, might point to the possibility of chemical antagonism between the two types inasmuch as both contain the dioxypyrimidine ring. There is, however, no biochemical evidence for any degradation of xanthines to pyrimidine derivatives in animals or man, and any suggestion of chemical antagonism between caffeine and the barbiturates must remain speculative at this time.

VI. CORAMINE

Coramine (nikethamide) is N,N-diethylnicotinamide (XII-15). It is synthesized from nicotinic acid by way of nicotinoyl chloride.



(XII-15)

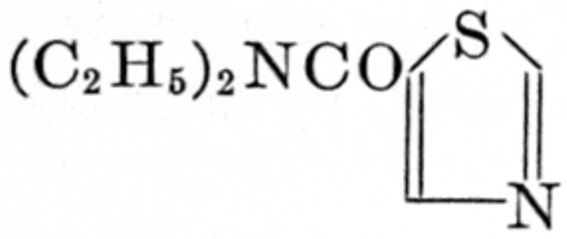
The main use of Coramine is to counteract excessive respiratory depression following the administration of barbiturates. Other amides of nico-

[17] Krüger and Schmid, *Z. physiol. Chem.*, **36,** 1 (1902).

[18] May and Dyson, *May's Chemistry of Synthetic Drugs*, 4th ed. Longmans, Green, New York, 1939, p. 14.

tinic acid (the dimethyl-, dipropyl-, diisobutyl- and diallylamides) are much less active. Regardless of this optimal position of Coramine, its analeptic effect is hard to explain. It may be that its rate of hydrolysis to nicotinic acid is especially favorable; however, the latter has no unusual stimulating effects. Coramine and other amides of this series do have a weak antipellagric action (see Chapter XXVIII).

Many other tertiary amides have been tested as analeptics, with the hope of improving upon the rather moderate activity of Coramine. The diethylamide of thiazole-5-carboxylic acid (XII-16) has been reported to be an effective analeptic agent. Its synthesis was prompted by a consideration of the isosteric relations between the pyridine and thiazole ring systems. Other examples include tetrahydropyran-4,4-dicarboxylic acid bis-diethylamide.

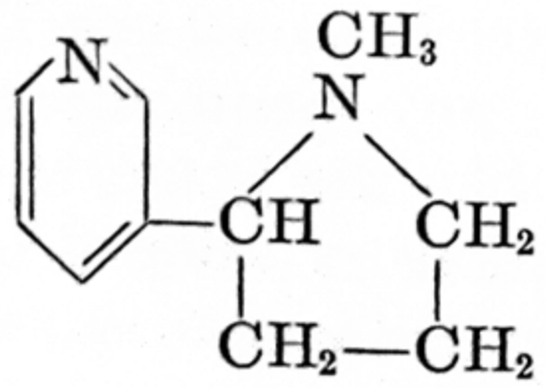


(XII-16)

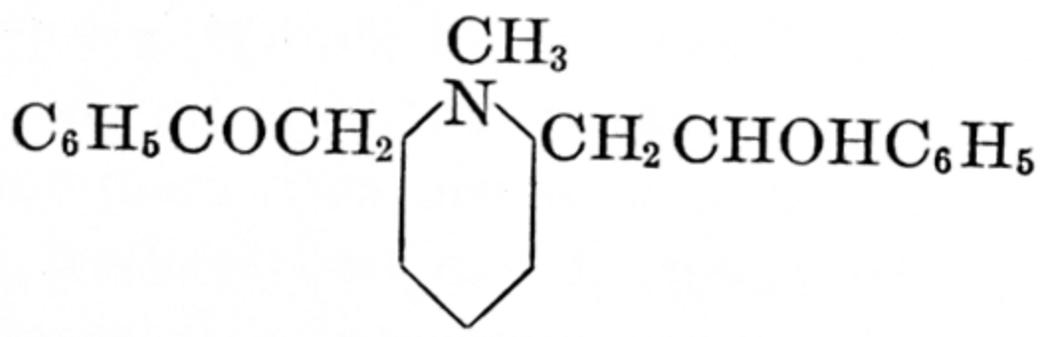
VII. ANALEPTIC INHIBITORS OF AUTONOMIC GANGLIA

Several alkaloids and drugs have the ability to stimulate and then persistently depress all autonomic nervous ganglia. They follow the complicated pattern set by nicotine, the prototype of this class of compounds. None of these substances are used any longer in medicine but they command a certain historical interest. Their stimulation of the respiratory centers would become valuable only at convulsive doses, and they have therefore no therapeutic significance.

Nicotine (XII-17), the main alkaloid of tobacco has retained a certain stimulating role since many smokers claim that it aids them to get over a feeling of tiredness. Lobeline (XII-18), the main alkaloid of *Lobelia* (Indian tobacco) has similar properties. Its analeptic effect has been put into use in experiments to resuscitate new-born infants.



(XII-17)



(XII-18)

The stimulating effect of cyanide and sulfide ions on aortic and carotid bodies is probably due to the known activation of various enzyme systems by these ions. The "lift" obtained by alcohol, and even by ether vapors,

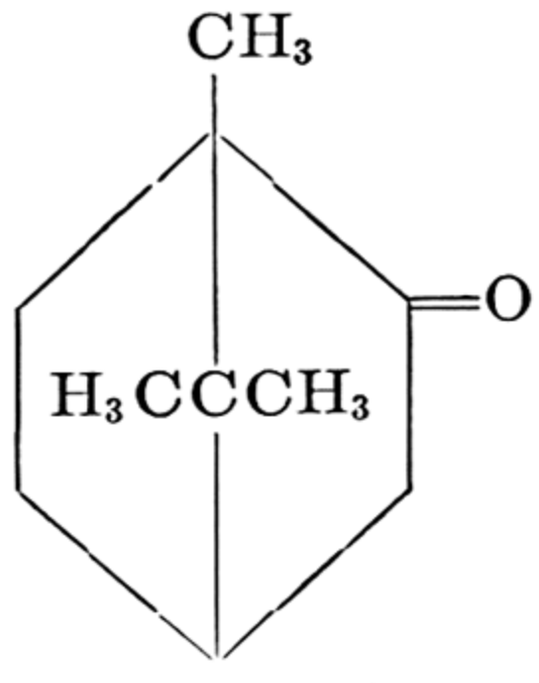
can be observed more clearly when these reagents are injected subcutaneously.

The rather incoherent assortment of analeptics listed in the preceding paragraphs would not be complete without mentioning some substances which produce similar effects by irritation. Smelling salts and ammonia belong in this group.

VIII. CAMPHOR

Camphor is a crystalline optically active component of the volatile essential oils obtained from the wood and bark of the oriental tree, *Cinnamomum camphora*. Racemic camphor is also manufactured synthetically. Its main use is in the plastics industry but its medicinal application has not yet been completely abandoned. Camphor is used as a circulatory and respiratory stimulant of rather uncertain effect. It has to be injected for this purpose and acts probably by eliciting reflexes to the painful local irritation it produces.

This irritating action on parenteral injection has led to a search for related compounds which might be free from this side-effect. Since camphor is a cyclic ketone (XII-19), other substances having this structural unit have been primarily considered. Attempts have also been made to prepare water-soluble derivatives of analogs of camphor.



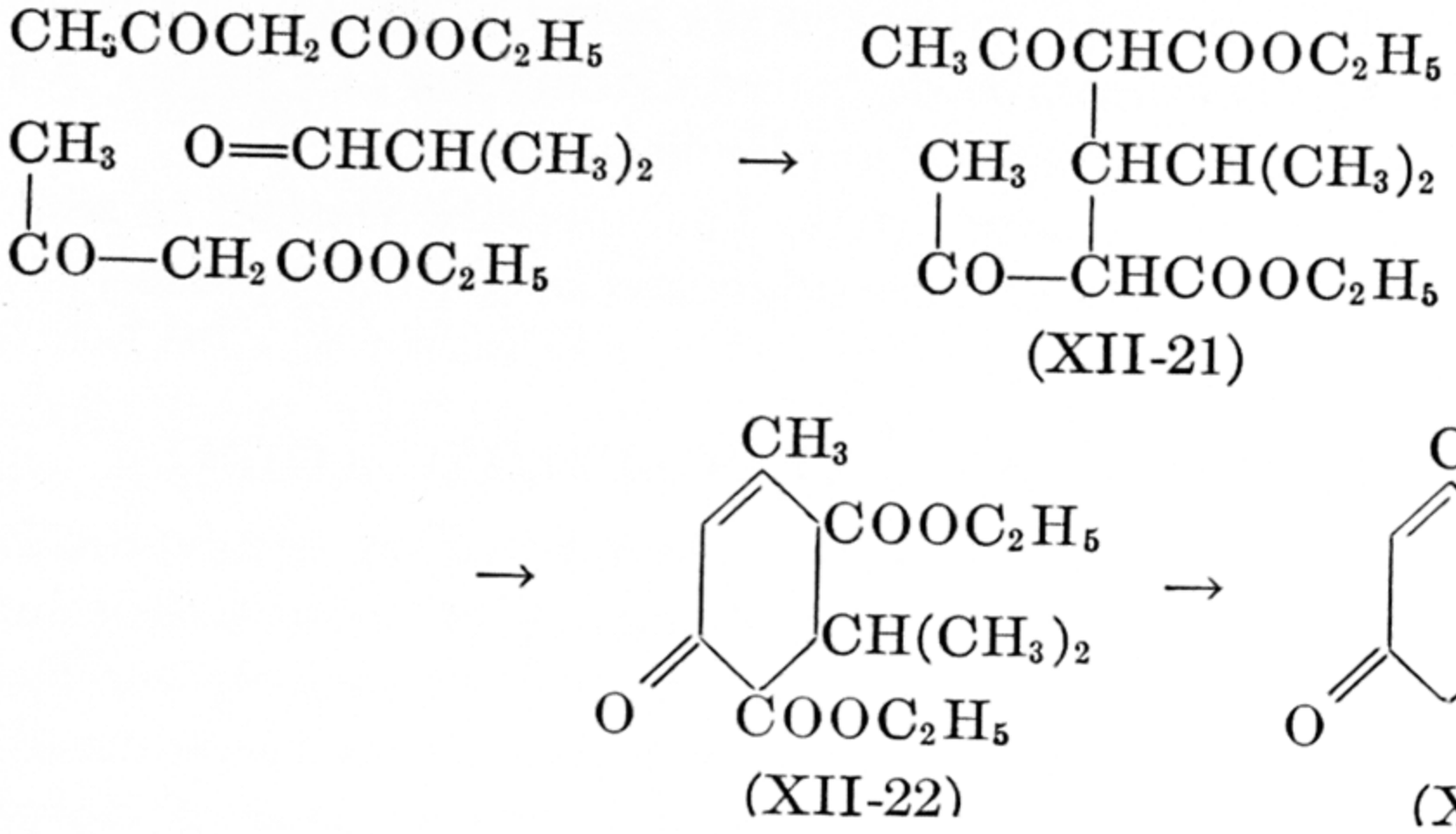
(XII-19)

The drug Hexetone (3-methyl-5-isopropylcyclohexene-2-one-1, XII-20) has been used as an analeptic but has barely any therapeutic significance today. It is isomeric with camphor and, like the latter, insoluble in water. However, it can be dissolved in solutions of salts of organic acids such as sodium benzoate, sodium salicylate, potassium isovalerate, etc.

Hexetone has been prepared[19] by condensing isobutyraldehyde with two moles of ethyl acetoacetate to ethyl α,α'-diacetyl-β-isopropylglutarate

[19] Bayer & Co., German Pat. 386,486 (1922).

(XII-21). The condensation is catalyzed by piperidine at low temperatures. Acids convert this ester to ethyl 3-methyl-5-isopropylcyclohexene-2-one-1-4,6-dicarboxylate (XII-22) which can be hydrolyzed and decarboxylated by acids or alkalis.



(XII-21)

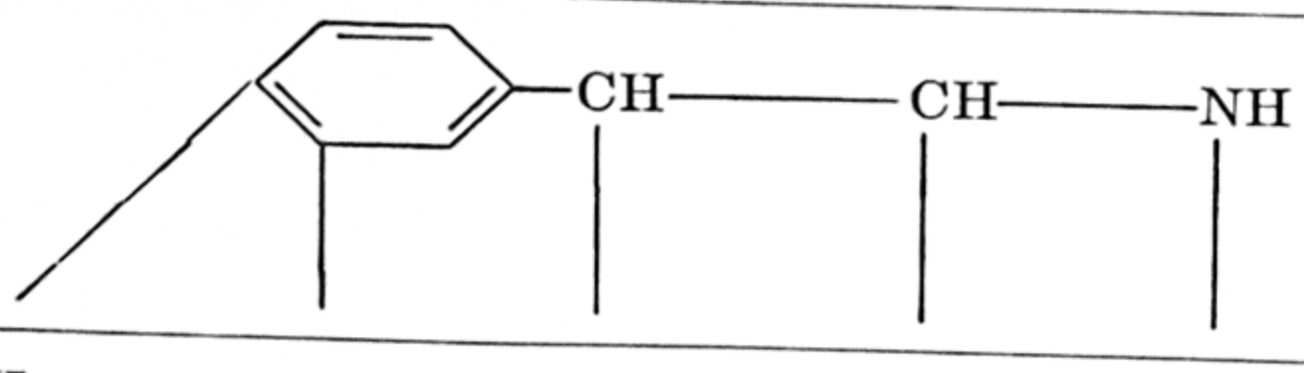
(XII-22)

(XII-20)

IX. PRESSOR DRUGS AS ANALEPTICS

A number of sympathomimetic amines have been found valuable as analeptics, and their ability to stimulate and excite the central nervous system overshadows in some cases their usefulness as pressor drugs and bronchodilator agents.

TABLE I. PHENETHYLAMINE DERIVATIVES USED AS ANALEPTICS



					Name
H	H	H	CH_3	H	Benzedrine
H	H	H	CH_3	H	Dexedrine
OH	H	H	CH_3	H	Paredrine
H	H	OH	CH_3	CH_3	Ephedrine
H	H	H	CH_3	CH_3	Desoxyephedrine

The criteria of analeptic activity in this group of amines appear to be resistance to enzymatic destruction, and in many cases branching at the β-carbon atom of the side chain, but exceptions to this rule are known. In high doses, these drugs cause convulsions like all other analeptics in chemically different series, and the production of hypertension and tachycardia

must be regarded as undesirable side-effects if the compounds are administered as analeptics. However, their hypertensive properties are material in increasing the blood supply to the brain, and this may be part of their analeptic mechanism.

The pressor amines used as analeptics are listed in descending order of potency in Table I. They will be discussed extensively in Chapter XIX, and the reader is referred to that section for details.

In addition, the non-aromatic drugs, Tuamine and Octine, as well as the imidazoline derivative Privine have been used as central nervous system stimulants.

X. CHLOROPHYLL AS A THERAPEUTIC AGENT

Chlorophyll, the green pigment of the plant kingdom, consists of two components, chlorophyll a and b. The chemistry of these magnesium-containing porphyrine complexes has been studied extensively by Hans Fischer and by Conant. Natural chlorophyll can be extracted readily from various leafy plants and has been introduced into medicine by Bürgi.[20]

Although it can barely be classified as an analeptic in the sense used in this Chapter, chlorophyll has been shown to improve many pathological conditions in a general way. Beneficial activity has been attributed to chlorophyll in the stimulation of growth, metabolism, respiration, hemopoiesis, in arteriosclerosis, hypertension etc. It has undoubtedly some synergistic effects in the granulation of tissues, and the healing of wounds and burns under the influence of antibiotics.

Chlorophyll is produced commercially by extraction of stinging nettles, spinach and alfalfa just before the flowering stage.

Rectal installation of chlorophyll has proved beneficial in cases of ulcerative and spastic colitis.[21] Perhaps the greatest use is made of chlorophyll as a deodorant. It absorbs odors by an unexplained mechanism, and can be taken orally to preclude various body odors, including those in perspiration, mouth and intestinal odors, odors from gangrene, etc.

[20] Bürgi, *Das Chlorophyll als Pharmakon*, Thieme, Leipzig, 1932. Rothemund, "Chlorophyll," in Glasser, *Medical Physics*, Year Book Publishers, Chicago, 1944.

[21] Rafsky and Krieger, *Rev. Gastroenterol.*, **15,** 549 (1948).

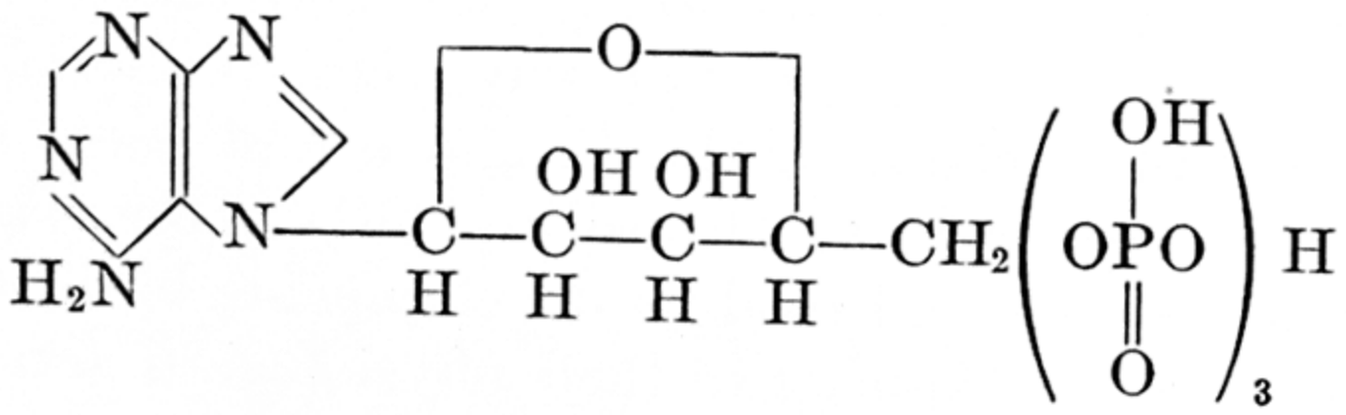
CHAPTER XIII

Cardiovascular Drugs

Among the drugs in this group are substances which stimulate or depress the heart by different mechanisms. Some of them alter the blood supply to the heart by constriction or dilation of blood vessels. They are used in many forms of heart disease, in angina pectoris, heart failure, cardiac edema, arrhythmias and auricular fibrillation, and in related conditions. They include particularly the nitrites, the digitalis aglucones, and khellin and visnagin. Certain drugs which act upon the heart indirectly by action on the central or peripheral nerves controlling heart action are treated in other Chapters of this volume.

The heart muscle, and the muscle cells of the artery walls are, like all other muscles, subject to the biochemical events which govern their ability to contract and relax. The contractile structure of muscle consists of a protein complex, actomyosin, which can be cleaved into myosin, a crystallizable protein, and another protein, actin. The latter exists in two forms, as globules and as long threads. The actin globules have a molecular weight of 70,000, the threads of 1,500,000. About twenty of the actin globules can unite to form one actin thread, and several threads associate to fibers. To these fibers are attached the long, thin colloidal myosin molecules in the actomyosin complex.

The reactions of this complex are slow. Activation leading to contraction is accomplished by the master catalyst, adenosine triphosphate (ATP) (XIII-1). Muscle without ATP cannot flex. The straight and stretched actomyosin filaments become unstable under the influence of ATP, lose their electric charge, dehydrate, shrink and fold up into shorter, more stable fibers containing less energy.



(XIII-1)

It may appear from the foregoing remarks set forth by Szent-Györgyi[1] in a lucid article that ATP could become an invaluable therapeutic tool in stimulating muscles and especially heart muscle. ATP is now available commercially, and encouraging results in conditions in which dysfunctioning of muscle is involved have been reported.

If, as it now seems likely, the endothermic nature of the triphosphate group in ATP is the source of energy for the contraction of muscle, any drug which supports the synthesis or accumulation of ATP should be musculotonic. It is as yet unknown whether the cardiotonic drugs and cardiovascular regulators discussed in this Chapter act by a mechanism involving ATP.

In addition to its effect on the heart muscle, ATP has been found to possess potent vasodilator action without much depressor side-effects.[1a] This property may aid by increasing the blood supply to the heart.

I. DIGITALIS

Plants of the order *Apocynaceae*, as well as *Liliaceae*, *Ranunculaceae* and *Scrophulariaceae* contain steroids which exert a pronounced and specific action on the heart muscle. The common pharmaceutical preparations consist of the dried seeds and leaves of *Digitalis purpurea* (purple foxglove). Other preparations come from the bulbs of the Mediterranean sea onion or squill (*Scilla maritima*), the seeds and barks of *Strophanthus* (*S. hispidus*, *S. oratus*, *S. kombe*) and other equatorial African plants.

The steroids from these plants are highly poisonous glycosides which can be hydrolyzed to non-saccharides and sugar-free components called cardiac aglycones or genins. The pharmacological activity of the cardiac glycosides resides in the aglycone portion, but the sugar component modifies their absorption and distribution in such a way as to bring out the maximum cardiotonic potency of these toxic materials.

1. Pharmacological Properties and Clinical Uses

The digitalis glycosides had been used for centuries as ordeal drugs like physostigmine (Chapter XXI) and as arrow poisons but their introduction into the therapy of heart disease did not materialize until 1785. In that year, the English botanist and physician Withering published a volume entitled "An Account of the Foxglove and Some of its Medical Uses; with Practical Remarks on Dropsy and Other Diseases". Withering foresaw many of the uses and modern developments of digitalis, although he misunderstood the mechanism of their physiological action. It is now

[1] Szent-Györgyi, *Science*, **110,** 411 (1949).
[1a] Folkow, *Acta Physiol. Scand.*, **17,** 311 (1949).

known that dropsy which responds to digitalis therapy results from cardiac dysfunction. Digitalis acts directly on the heart muscle fiber. It increases the output of blood volume per stroke by strengthening the force of systolic contraction and consequently emptying more completely the ventricle. This permits the heart muscle to take care of the next return of venous blood and to rest between the phases of the cardiac cycle. Heart rate is slowed in the weak and irregular contractions of auricular fibrillation, and diastolic heart size is decreased. By decreasing venous pressure, fluid accumulating between the tissues can now re-enter the circulatory system and reach the kidney where it is excreted. Digitalis has thus a diuretic effect which increases its value as the drug of choice in congestive heart failure. In addition, heart failure without abnormal rhythm or rate is also aided by digitalis.

The digitalis glycosides bring only temporary relief, and must be administered orally during the whole course of the disease, that is, usually over the remaining life span of the patient. Parenteral administration (digitalization) is used only in emergencies. The toxic dose of digitalis lies close to the therapeutic dose, and nausea, salivation and other common manifestations of the toxicity syndrome lead up to incoordinated contraction of the heart (ventricular fibrillation), the usual cause of fatal digitalis poisoning. The dose inducing this condition in 50% of the animals (LD_{50}) forms one of the standards in the bioassay of the medicinal drug. The standard test is to inject the drug intravenously into anesthetized animals (cats) and increasing the dose until the LD_{50} is reached.[2] Another test is based on the effect of glycosides on the isolated heart muscle.

No other muscle is affected nearly as much by digitalis as is the heart. Comparatively huge doses of the drug mixture are only musculotonic in a non-specific manner.

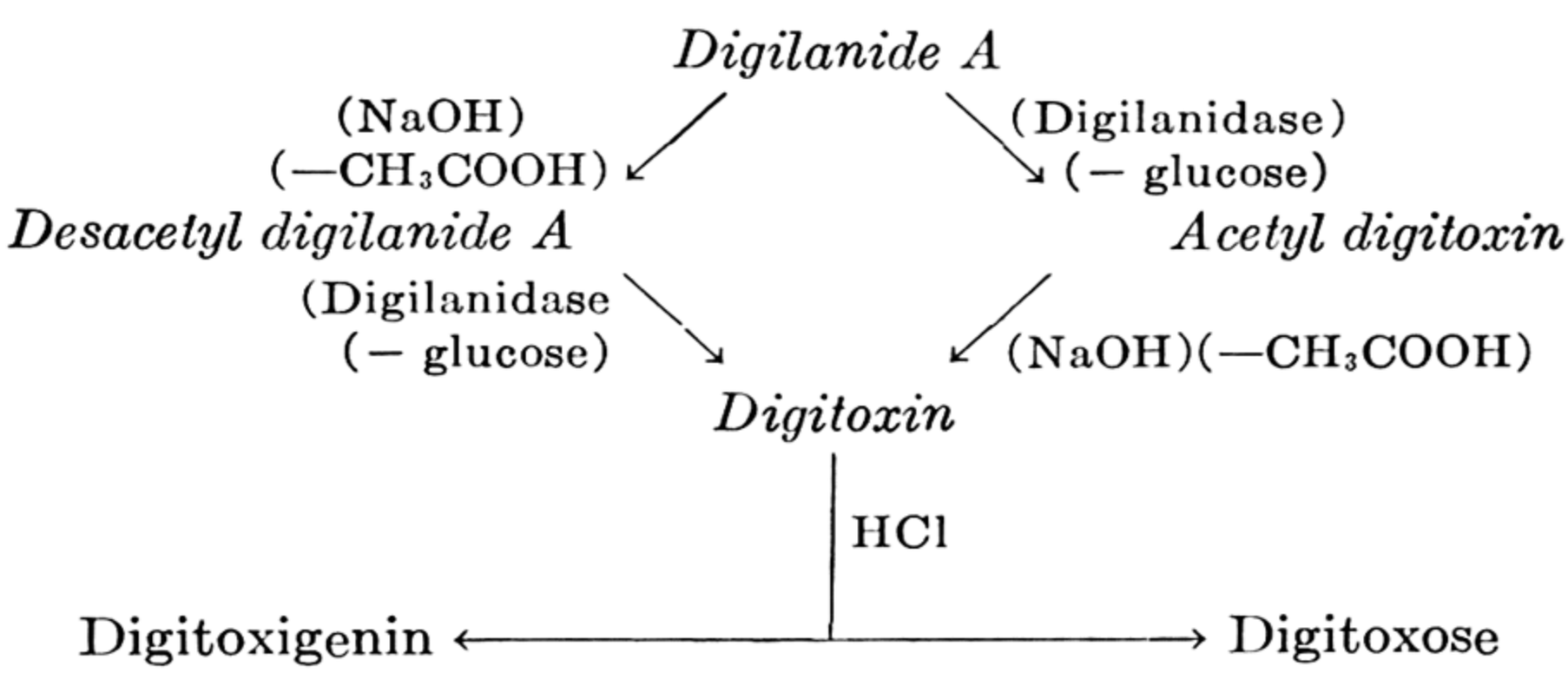
2. Chemistry

The poisonous principles of digitalis occur in the drug in very small quantities, and are very difficult to purify. Several chemically similar compounds are usually found in the same plant, and are furthermore contaminated with other, cardiotonically inactive steroids of the saponin class. The separation of the individual glycosides, and their crystallization as pure substances is complicated further by the ease with which the sugar moieties are lost hydrolytically. These difficulties are the cause of the continued use of the crude drug mixture in therapy instead of selecting pure digitalis glycosides for special medicinal purposes. Fortunately, the mixture of the heart poisons as it is present in the dried plant material exerts

[2] Chen, *Ann. Rev. Physiol.*, **7,** 681 (1945). Compare Wollenberger, *J. Pharmacol. Exptl. Therap.*, **97,** 311 (1949).

an overall cardiotonic effect which does not differ substantially from that of its individual constituents. This is due, in part, to the fact that hydrolysis of two or more glycosides usually yields the same active aglycone.

The methods of separation and purification of the cardiac glycosides have been reviewed by Fieser and Fieser.[3] Their article also gives a detailed picture of the chemical work of Windaus, and of Jacobs which had led to the now accepted structural formulas of these drugs. The careful investigations of Stoll have clarified the nature of several of the unaltered, original heart poisons.[4] The older studies in this group had regarded the glycosides digitoxin, gitoxin and digoxin as the original plant products but had overlooked the fact that hydrolytic enzymes present in the plant materials had cleaved the original glycosides even under mild extraction conditions. By deactivating the enzymes, for instance, digilanidase, the genuine glycosides (digilanides) could be preserved and were found to be hydrolyzable to glucose, acetic acid, and what had once been regarded as the original glycosides. These latter secondary products were now reclassified as progenins, since further hydrolysis cleaved them to the aglycone (or genin) and a specific carbohydrate. These steps shall be demonstrated for the case of digilanide A, the precursor of digitoxin. In this



scheme, digilanide A is the original plant glycoside, digitoxin a progenin, digitoxigenin an aglycone, and digitoxose the specific sugar of this series.

The acid hydrolysis of the progenins is carried out best in methanol[5] or acetone[6] medium. Aqueous hydrochloric acid requires such drastic condi-

[3] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed. Reinhold, New York, 1949, pp. 507–577.

[4] Stoll and Kreis, *Helv. Chim. Acta*, **16,** 1049, 1390 (1933); **17,** 595 (1934); **18,** 120 (1935); *Z. Physiol. Chem.*, **235,** 249 (1935). Stoll, *J. Pharm. Pharmacol.*, **1,** 849 (1949).

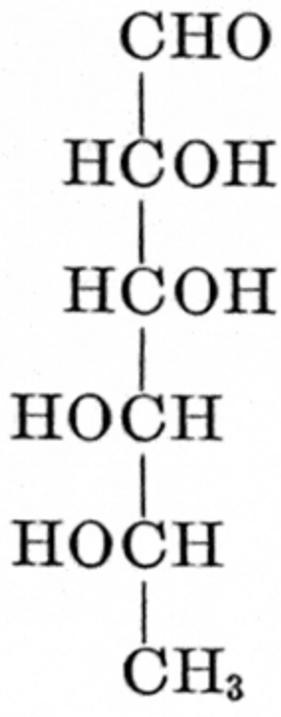
[5] Voss and Wachs, *Ann.*, **522,** 240 (1936). Voss and Vogt, *Ber.*, **69,** 2333 (1936).

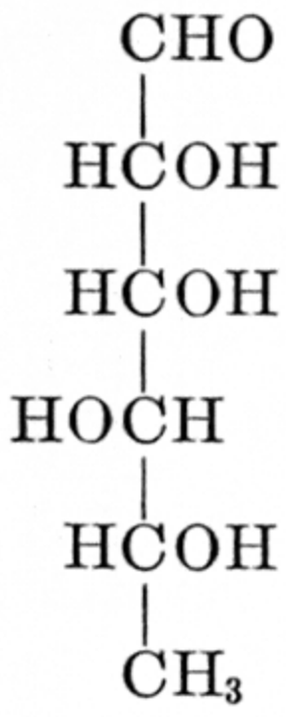
[6] Mannich and Siewert, *Ber.*, **75,** 737 (1942).

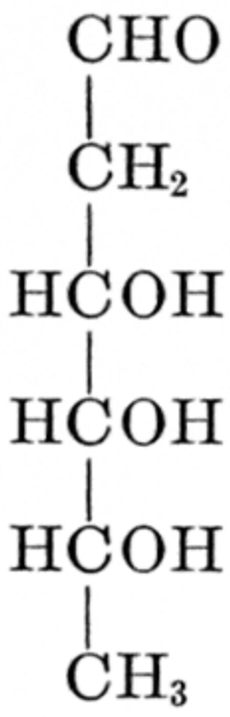
tions in some cases that the aglycones are dehydrated with the loss of alcohol groups.

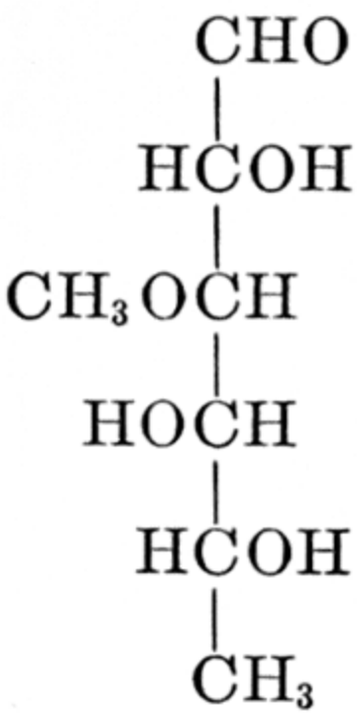
a. The Monosaccharide Moieties

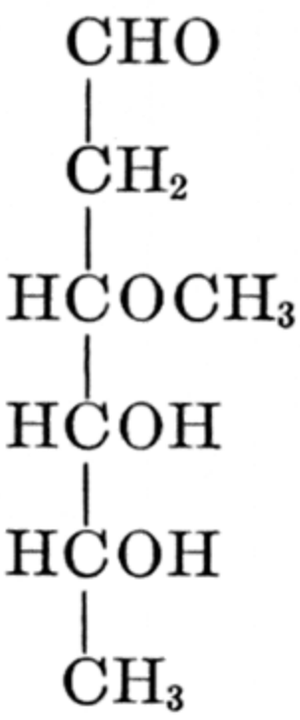
The sugars obtained from the progenins are glucose, and the desoxyhexoses rhamnose (XIII-2); its 5-epimer, antiarose (XIII-3); digitoxose (XIII-4); digitalose (XIII-5); cymarose (XIII-6); and similar 2-desoxy-, 2,6-bisdesoxyhexoses or their methyl ethers. Only glucose and rhamnose occur in other materials as well; all the other monosaccharides in this group are found exclusively in the digitalis glycosides.


(XIII-2)


(XIII-3)


(XIII-4)


(XIII-5)


(XIII-6)

b. The Aglycones (Genins)

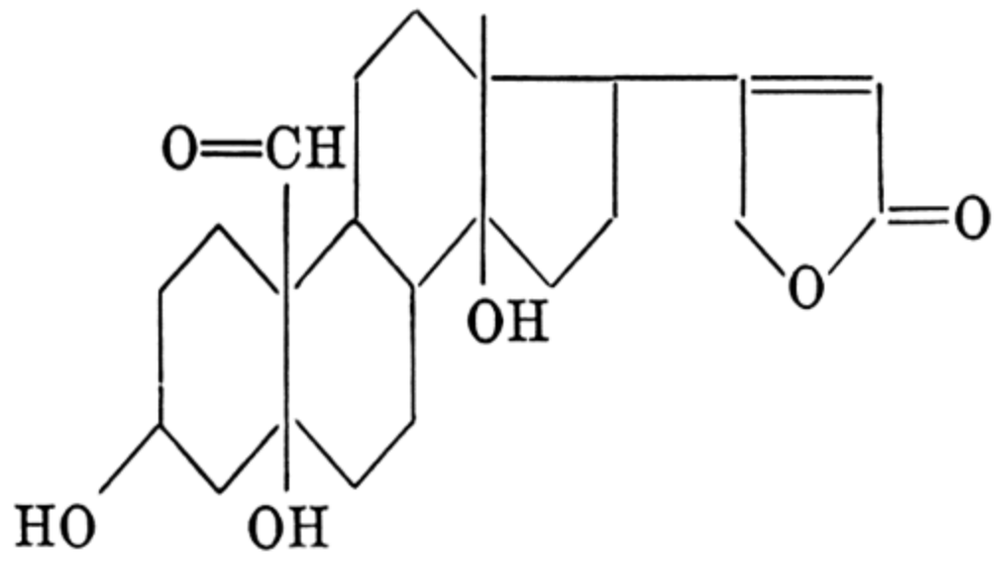
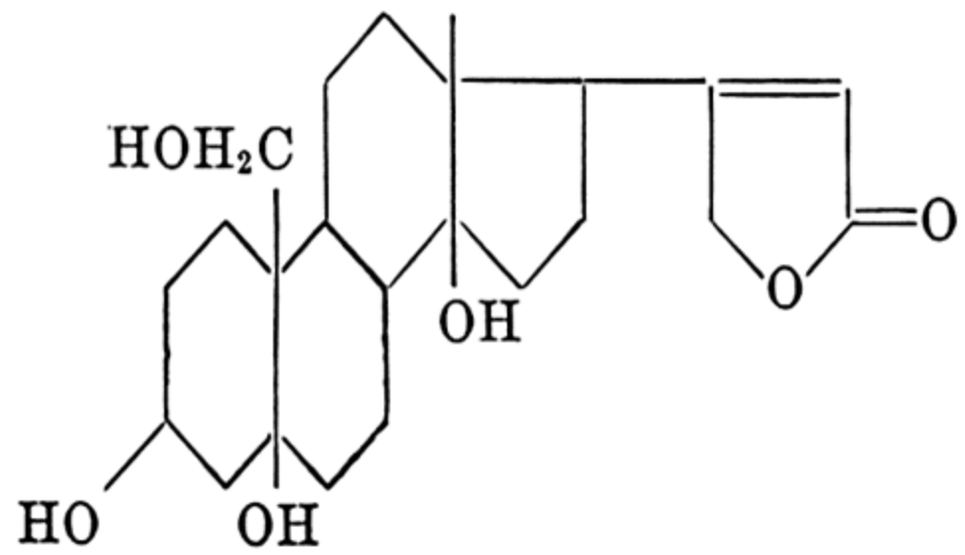
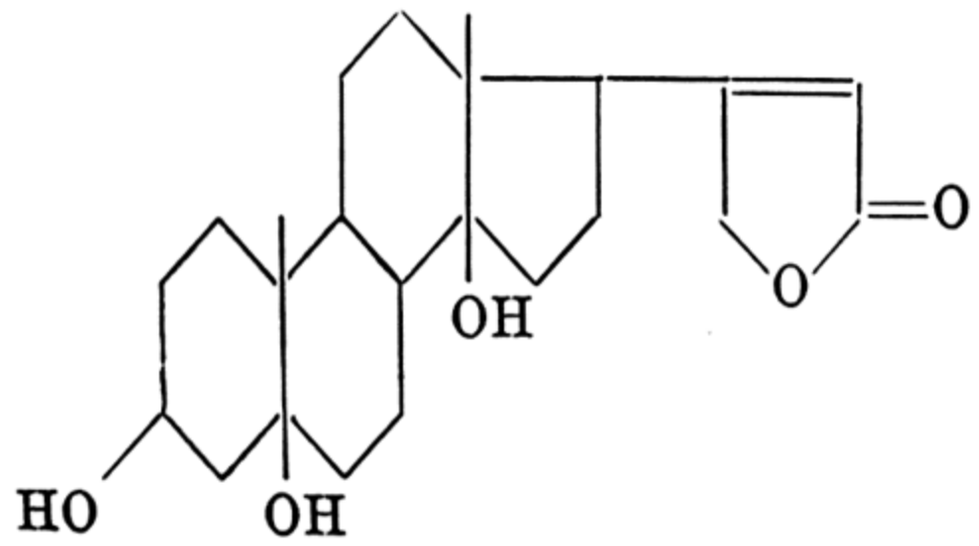
(1) Structure

The steroid substances remaining as the end-products of the hydrolytic cleavage of digitalis and strophanthus glycosides have the general formula $C_{23}H_{34}O_{4-8}$. They are derivatives of perhydrocyclopentanophenanthrene, and all carry an unsaturated lactone group in position 17. They are substituted by alcohol groups in different positions, mainly in position 3, 5, 12, and 14. Most of the aglycones contain angular methyl groups in positions 10 and 13 but aldehyde or primary alcohol groups are also encountered in position 10.

The sterical configuration of the cardiotonic aglycones has been studied extensively. The alcohol groups at C_3 and C_5 and the lactone rings have the β-configuration, the junctures of rings A/B are usually cis, those of rings B/C trans. However, the C/D-ring configuration is cis while it is trans in the sterols. This gives the β-orientation to any hydroxyl group that may be present at C_{14}.

The names and structural formulas of the cardiotonically most important aglycones are listed in Table I. The other columns give the glycosides (or, in a few cases, the progenins) from which the aglycones are derived, and the names of the monosaccharides found in the corresponding glycosides.

TABLE I. SOME CARDIAC GYCOSIDES, AGLYCONES AND SACCHARIDE COMPONENTS

Aglycone(Genin)	Structure	Glycosides	Monosaccharides
Strophanthidin		Convallatoxin Cymarin Convalloside K-Strophanthoside	Rhamnose Cyamarose Rhamnose + glucose Cymarose + glucose
Strophanthidol		Cymarol	Cymarose
Periplogenin		Periplocymarin Emicymarin Periplocin	Cymarose Digitalose Cymarose + glucose

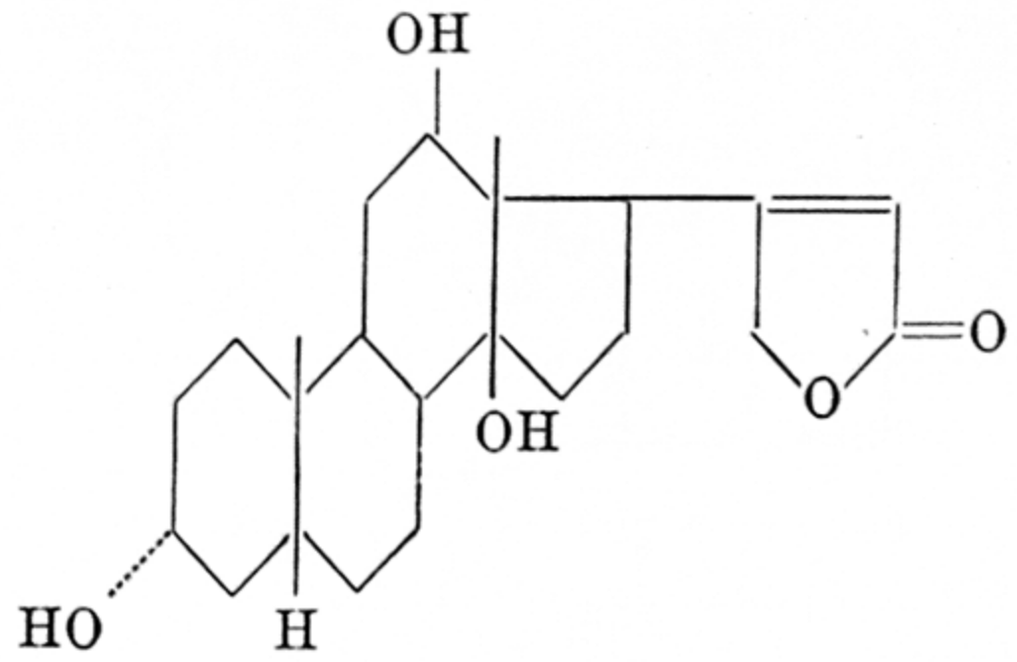
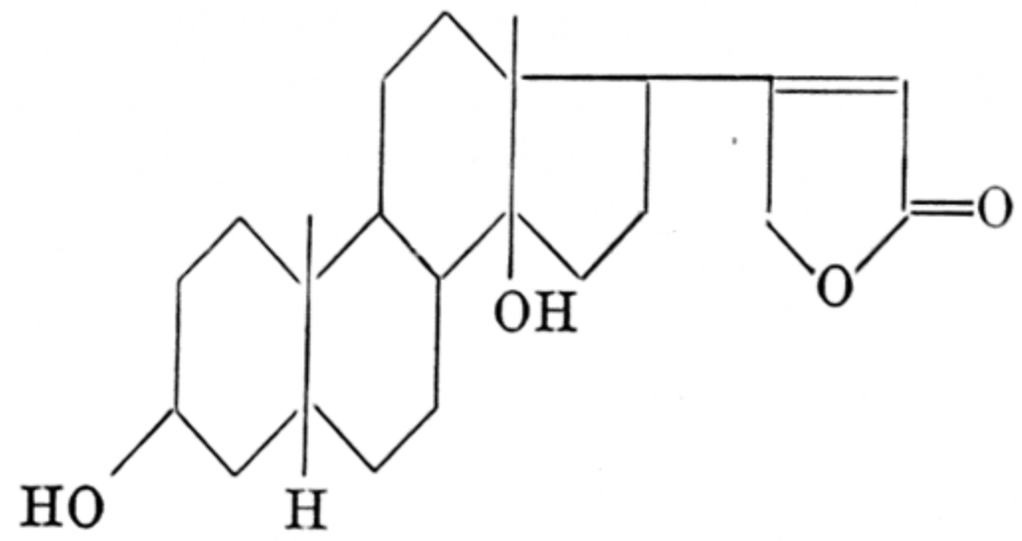
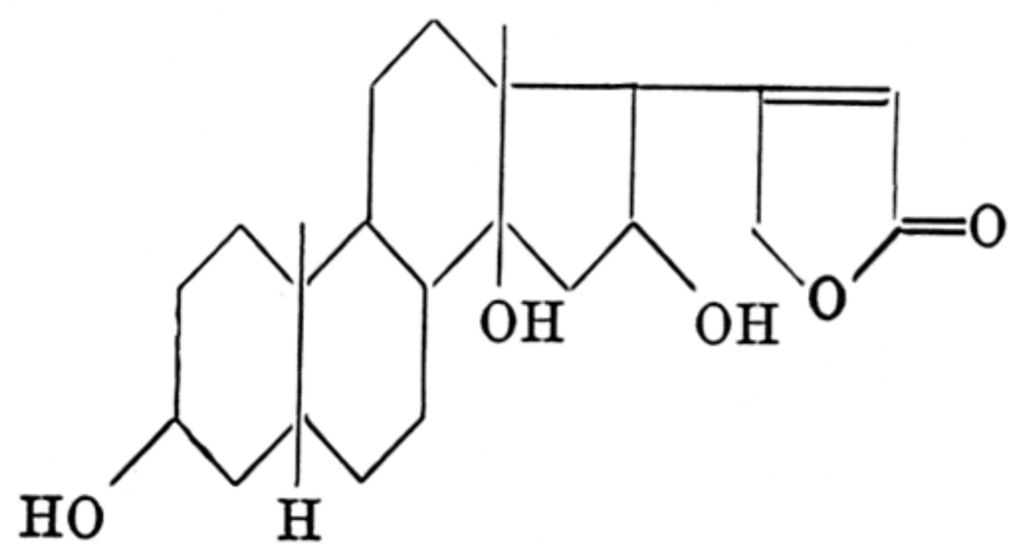
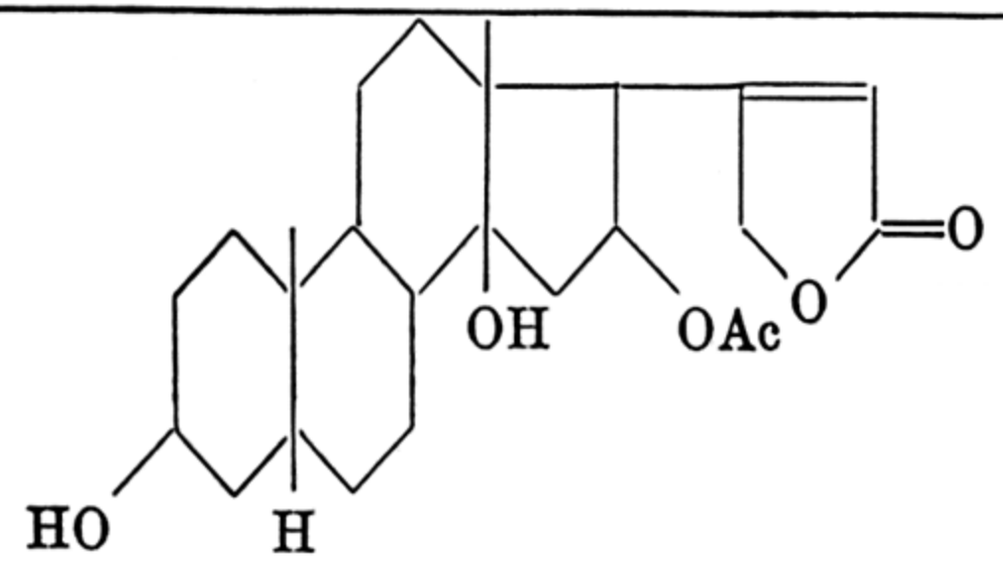
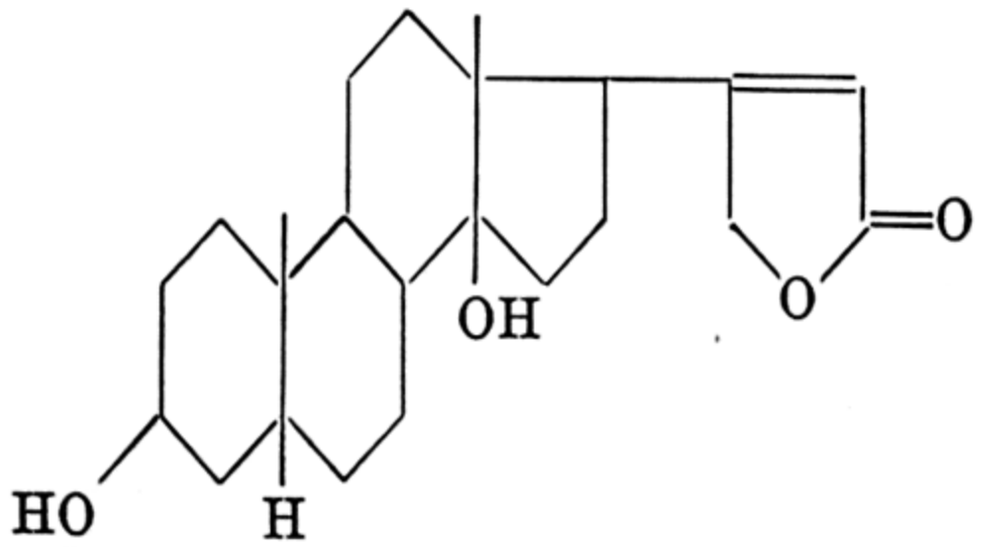
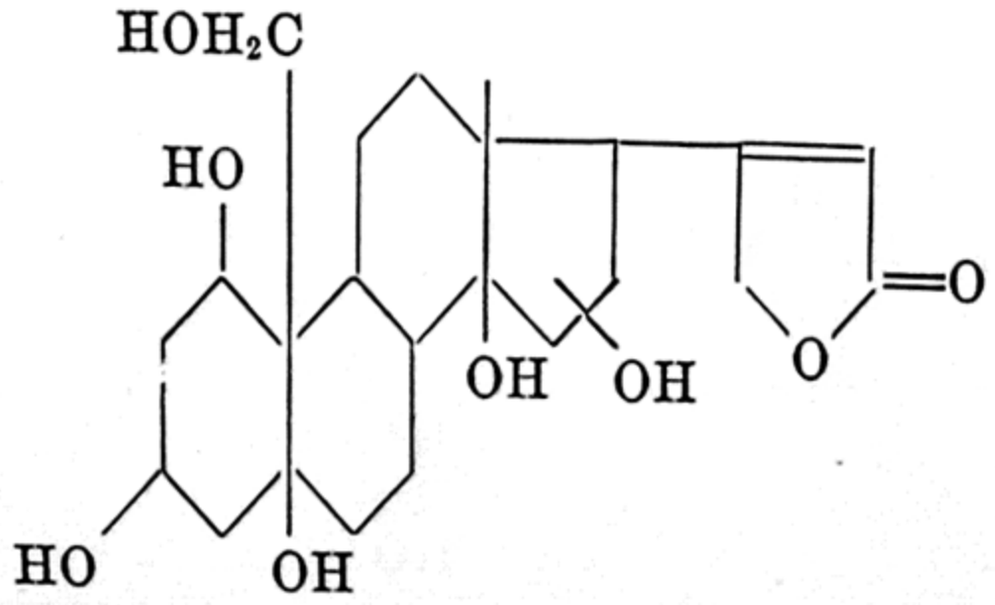
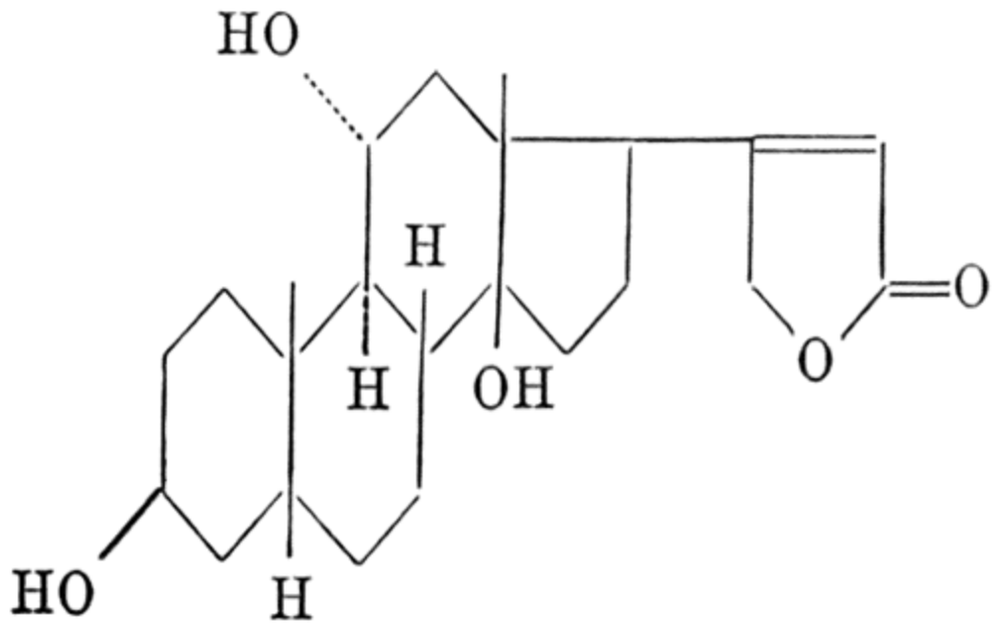
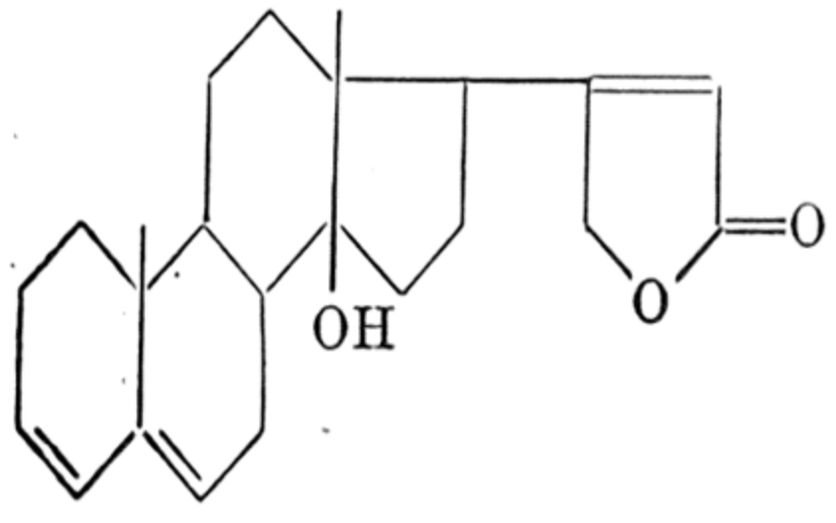
Digoxigenin		Digoxin Digilanide C	Digitoxose Digitoxose + glucose
Digitoxigenin		Somalin Digilanide A Digitoxin Thevetin	Cymarose Digitoxose + glucose Digitoxose Thevetose + glucose
Gitoxigenin		Gitoxin Digilanide B	Digitoxose Digitoxose + glucose

Table Continued

TABLE I (*Continued*)

Aglycone(Genin)	Structure	Glycosides	Monosaccharides
Gitoxigenin-α16-acetate		Oleandrin	Oleandrose
Ouzarigenin[7]		Uzarin	Glucose
Ouabagenin		Ouabain	Rhamnose

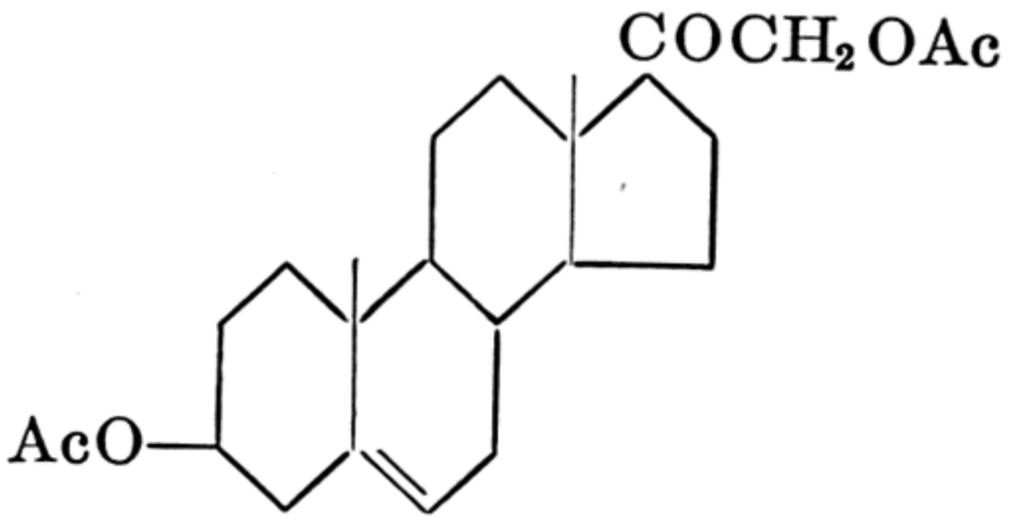
Sarmentogenin		Sarmentocymarin	Sarmentose
Scillaridin A[8]		Scillaren A	Rhamnose + glucose

(2) *Synthesis of Cardiac Genins*

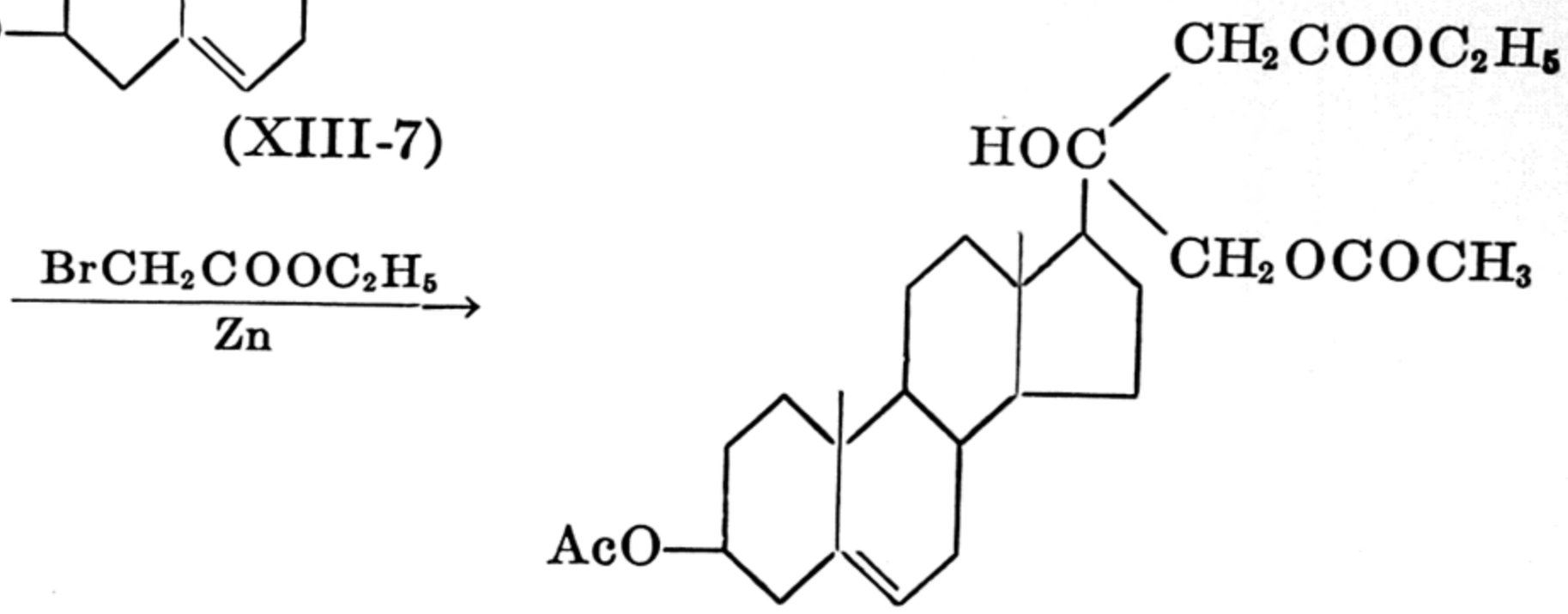
Synthetic experiments for the construction of unsaturated steroid lactones, starting from readily accessible steroid hormonal substances, have been reported by Elderfield, by Ruzicka and by Reichstein.[9] Apart

(a) $RCOOH \rightarrow RCOCl \rightarrow RCOCHN_2 \rightarrow RCOCH_2OAc$

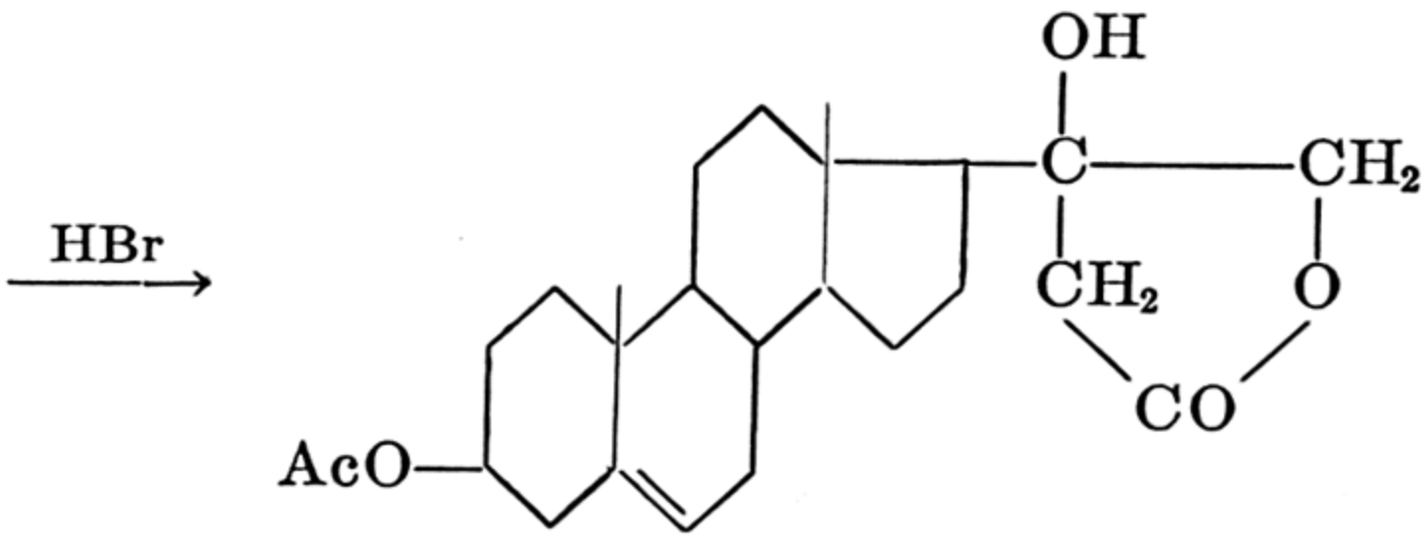
(b) $RCOCH_3 \rightarrow RCOCH_2OAc$



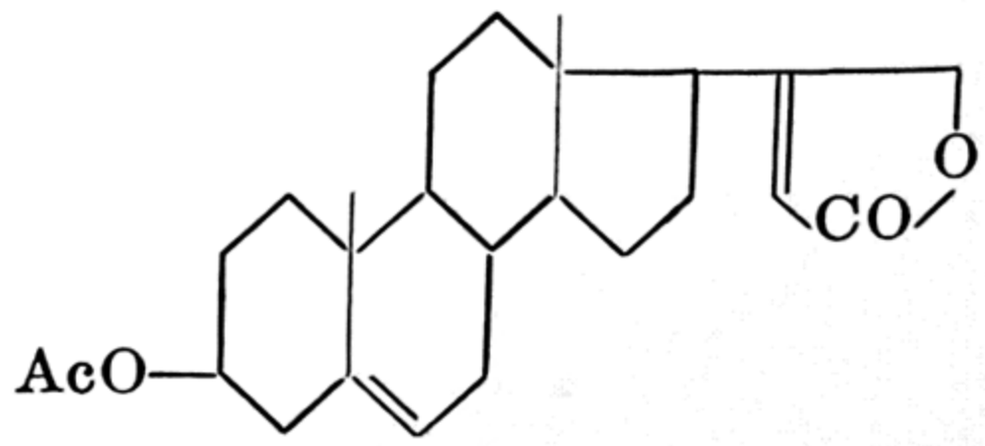
(XIII-7)



(XIII-8)



(XIII-9)



(XIII-10)

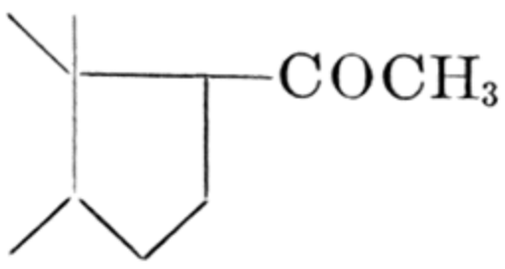
[7] Known only as the anhydroaglycone which has lost H_2O (OH at C_{14}) at C_{14}—C_{15}.
[8] Known only as the anhydroaglycone which as lost H_2O (OH at C_3) at C_3—C_4.
[9] See the review by Turner, *Chem. Revs.*, **43,** 1 (1948).

from the scientific interest attached to these syntheses, they could ultimately achieve the desirable practical goal of making available pure cardiotonic steroids which would not have to be standardized by bioassays. So far, none of the naturally occurring cardiac poisons has been synthesized.

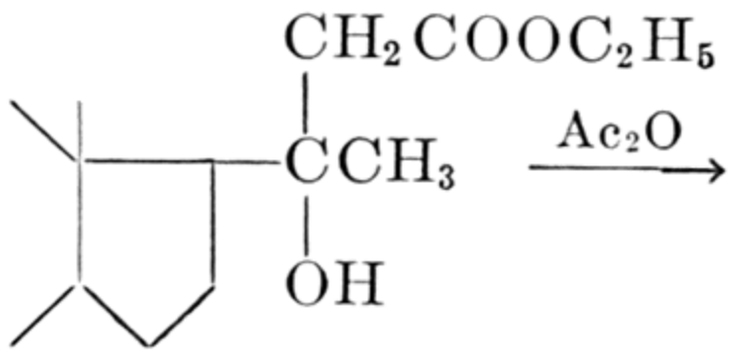
As an example of syntheses of steroid unsaturated lactones, the preparation of 3(β)-acetoxy-Δ^5-etiocholenylbutenolide (XIII-10) shall be described. It starts from 3(β),21-diacetoxy-Δ^5-pregnen-20-one (XIII-7) which in turn can be prepared (a) either from the appropriate bile acid by way of the acid chloride and diazoketone, or (b) from the corresponding methyl ketone by oxidation with lead tetraacetate. The acetoxy ketone (XIII-7) is subjected to a Reformatsky reaction with ethyl bromoacetate and zinc, and the resulting hydroxy ester (XIII-8) is cyclized and dehydrated to the unsaturated lactone (XIII-10). The intermediate hydroxylactone (XIII-9) can be isolated occasionally.

The Reformatsky reaction can also be performed with 17-acetyl steroids (XIII-11). The hydroxy ester from this reaction (XIII-12) is then dehydrated, and the methyl group of the crotonic ester derivative (XIII-13), activated by the conjugated system, can be oxidized to —CH_2OH with selenium dioxide; the primary alcohol formed lactonizes immediately.

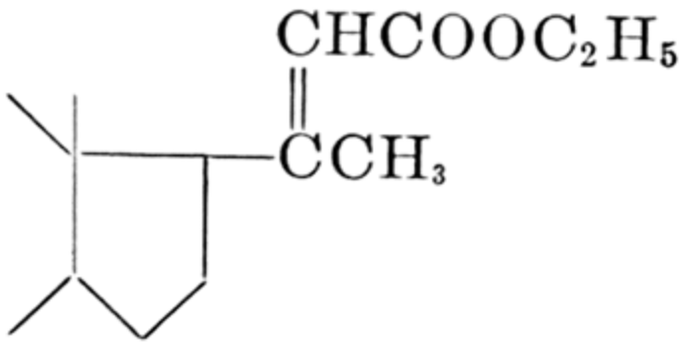
The yields are much more satisfactory in a modification of this synthesis[10] which subjects the diazoketone (XIII-14) directly to a condensa-



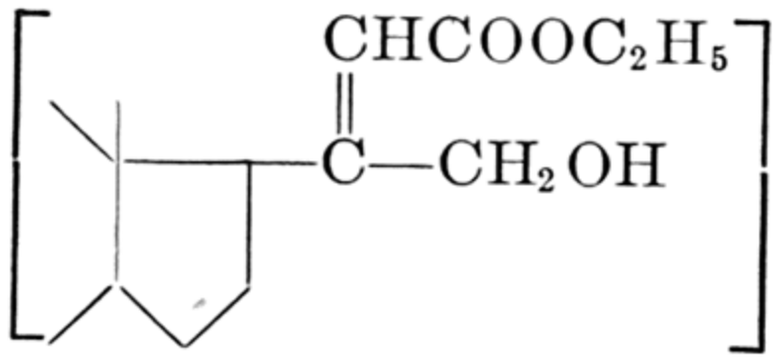
(XIII-11)

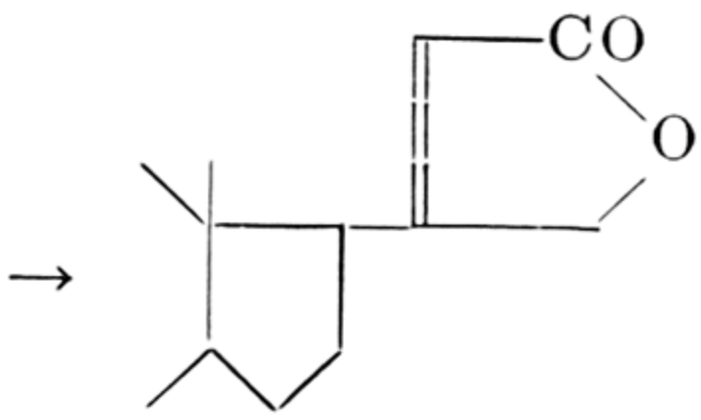


(XIII-12)



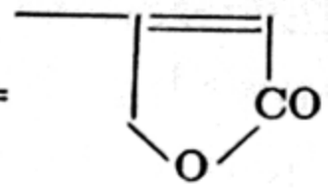
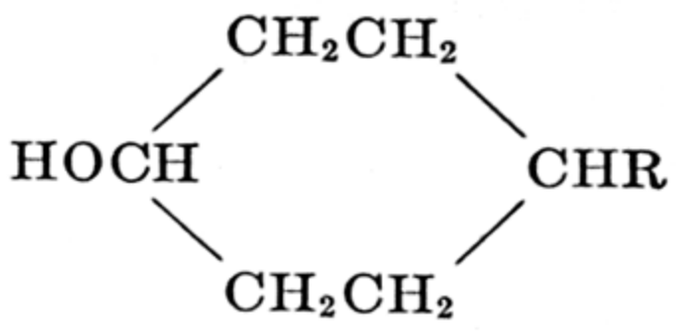
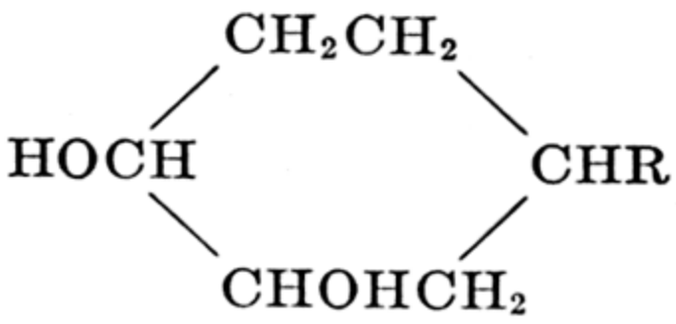
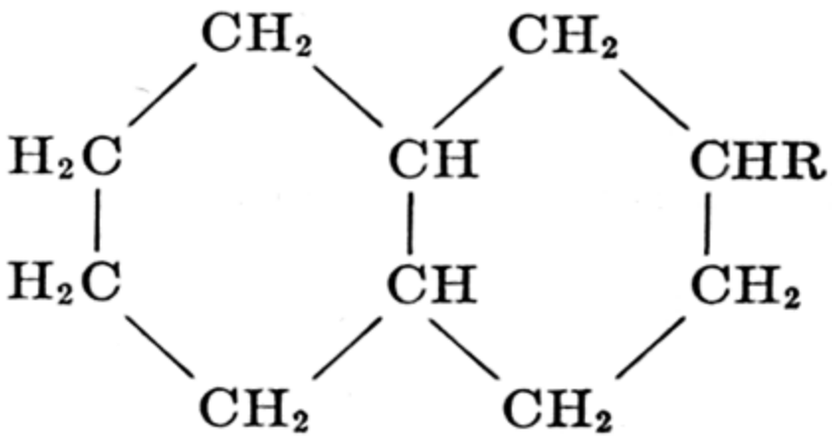
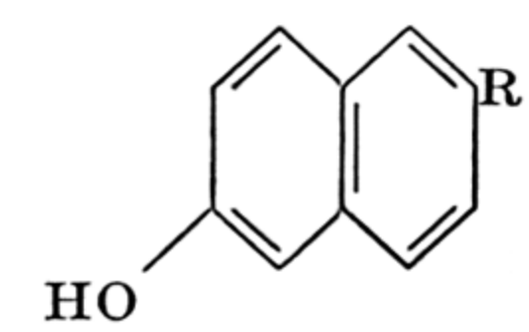
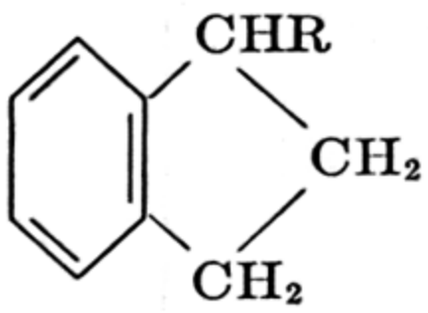
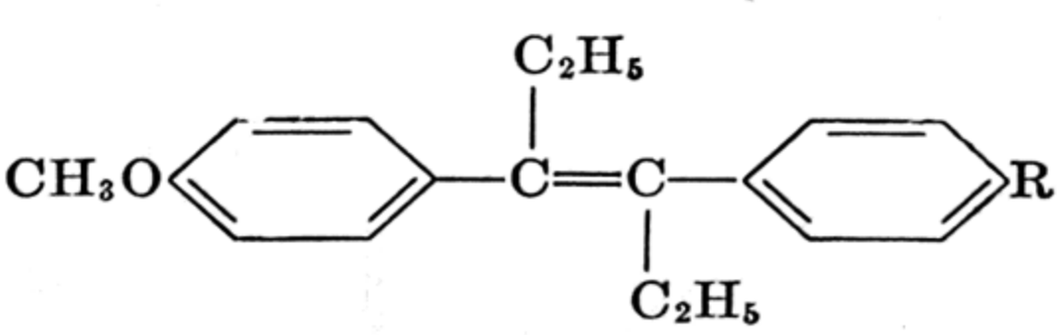
(XIII-13)





[10] Plattner and Heusser, *Helv. Chim. Acta*, **28,** 1044 (1945). Plattner, Heusser, and Kulkarni, *ibid.*, **31,** 1822 (1948).

TABLE II. SIMPLE α,β-BUTENOLIDES SYNTHESIZED AS MODELS FOR NATURAL DIGITALIS AGLYCONES

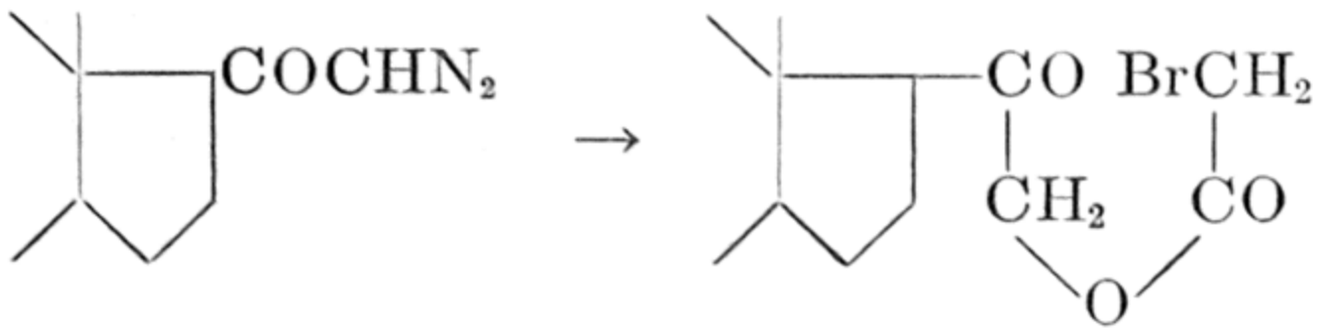
R = 	Name of α,β-Butenolide	Reference
	4-Hydroxycyclohexyl-	12
	3,4-Dihydroxycyclohexyl-	13
C_6H_5R	Phenyl-	14
p-HOC_6H_4R	*p*-Hydroxyphenyl-	15
m-HOC_6H_4R	*m*-Hydroxyphenyl-	15
	Decahydro-2-naphthyl-	16
	6-Hydroxy-2-naphthyl-	16
	1-Hydrindanyl-	16
	4-Methoxy-4′-(α,β-diethylstilbene)-	17

[11] Meystre and Miescher, *Helv. Chim. Acta*, **27,** 1153 (1944). Plattner and Uffer, *ibid.*, **28,** 1049 (1945).

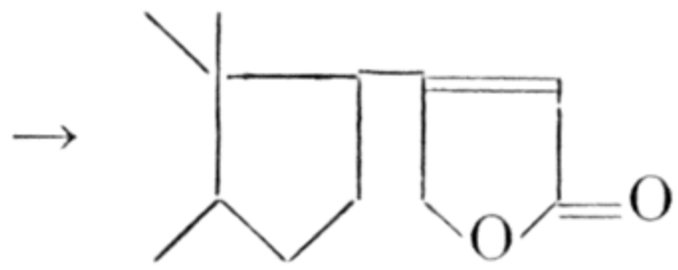
[12] Hardegger, Plattner, and Blank, *Helv. Chim. Acta*, **27,** 793 (1944).

[13] Hardegger, *ibid.*, **29,** 1195 (1946).

tion with bromoacetic acid. The bromo compound (XIII-15) can be lactonized in good yields under the influence of zinc and ethyl bromoacetate, perhaps by an intermolecular mechanism.

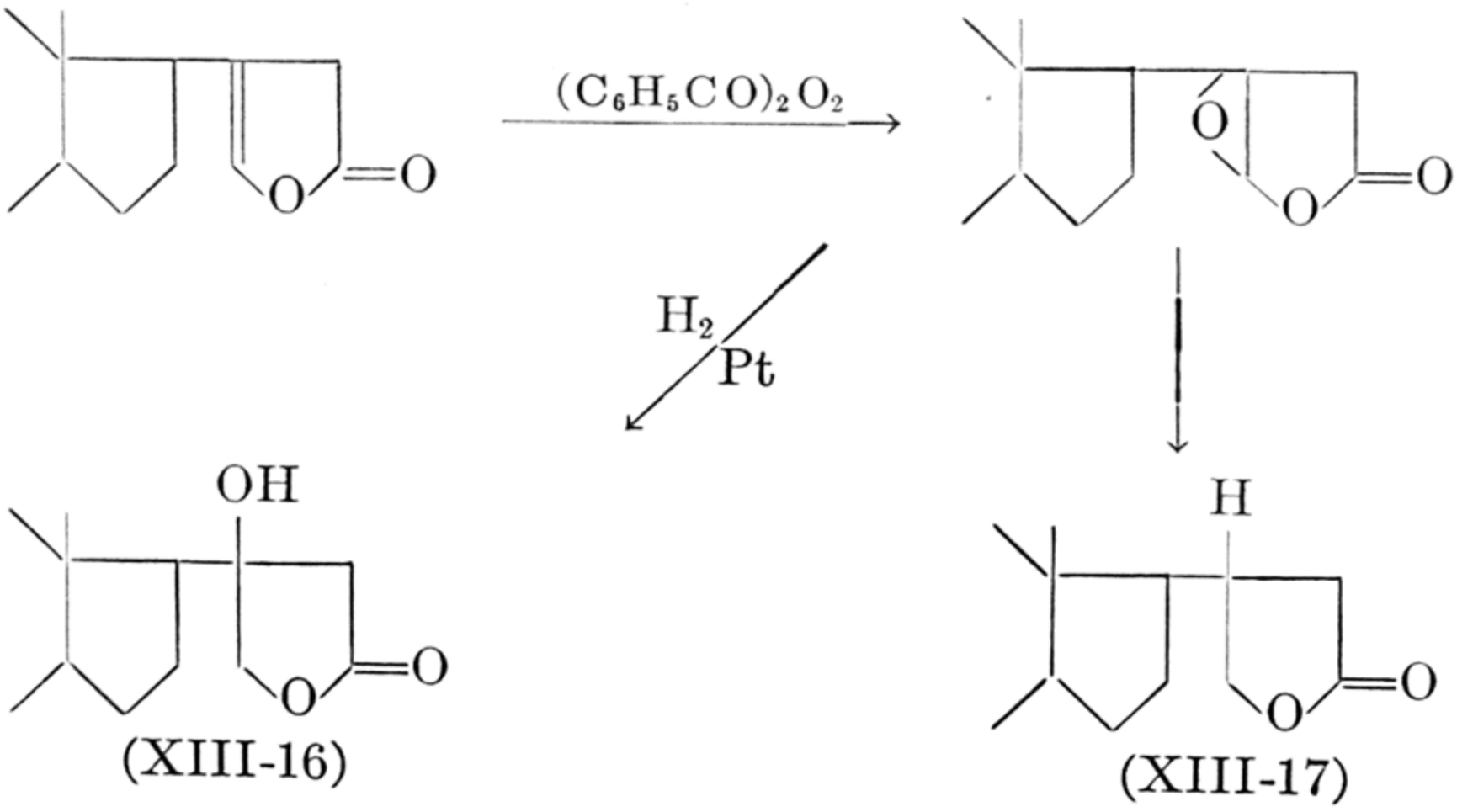


(XIII-14) (XIII-15)



The double bond in the lactone rings of the synthetic lactones is not located necessarily in the same position as in the natural aglycones but hydrogenation gives saturated lactones, and several of these have proved identical with the reduction products of the natural genins.

Two of the synthetic unsaturated lactones obtained by methods described above have been converted to the respective glucosides and maltosides.[11] The synthetic methods have also been applied to simpler α,β-butenolides in which the lactone group is attached to aromatic nuclei, hydroxy substituted cyclohexyl groups serving as models for steroid systems, and other saturated rings. There has been no report about the cardiac activity of these model compounds.



(XIII-16) (XIII-17)

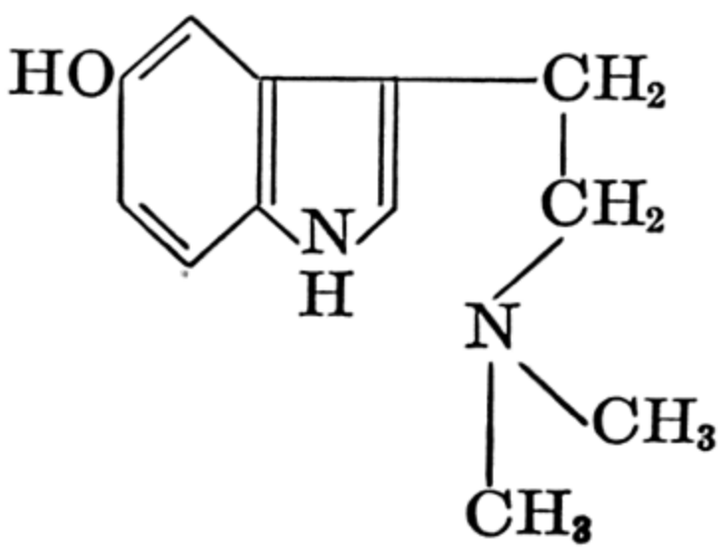
[14] Linville and Elderfield, *J. Org. Chem.*, **6,** 270 (1941).
[15] Marshall, Kuck, and Elderfield, *ibid.*, **7,** 444 (1942).
[16] Knowles, Kuck, and Elderfield, *ibid.*, **7,** 374 (1942).
[17] Linnell and Said, *J. Pharm. & Pharmacol.*, **1,** 151 (1949).

Alcoholic hydroxyl groups have been introduced into synthetic analogs of cardiac aglycones by methods used in other steroids. For example, peracids can be added to the C_{14}–C_{15} double bond, and hydrogenation of the epoxide furnishes C_{14} alcohols. The position of the alcoholic hydroxyl is deduced from its resistance to acetylation and to oxidation with chromic acid. Besides the alcohol (XIII-16), a deoxygenated derivative (XIII-17) is also obtained. The reaction products must be separated chromatographically.

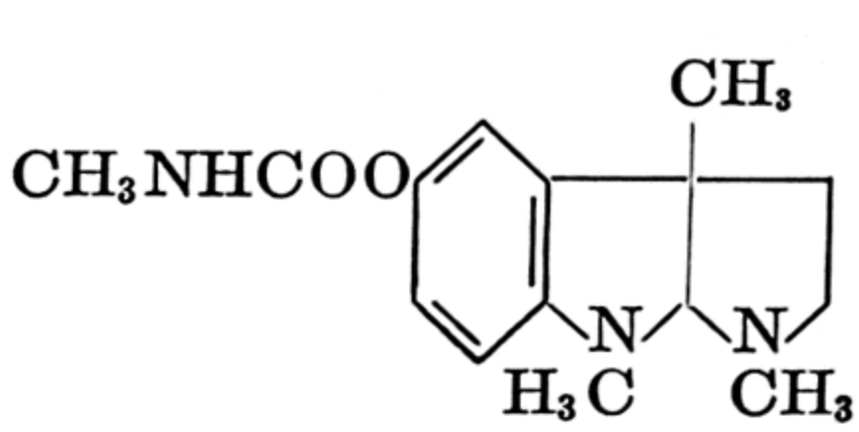
3. Toad Poisons[18]

The skin glands of the poisonous toad (*Bufa*) secrete a venom which has been used in the Orient for the stopping of bleeding and as an analgetic, and in Europe as a remedy for dropsy prior to the introduction of digitalis. The venom has a cardiotonic and toxic action of the same magnitude as the foxglove drug.

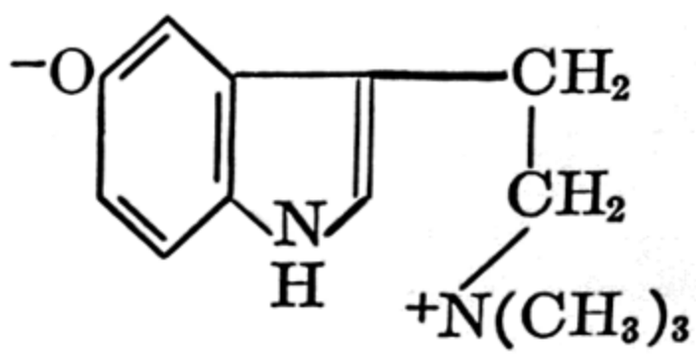
The hemostatic pressor, and perhaps the analgetic properties of toad venom are caused by a high percentage of epinephrine, bufotenine (XIII-18), and bufotenidine (XIII-19). Bufotenin is 5-hydroxy-N,N-dimethyltryptamine, and bufotenidine is its betaine. Both compounds have been synthesized for comparison with the authentic natural materials.[19] One cannot overlook the structural similarity of bufotenine and the cholinergic calabar bean alkaloid, physostigmine (XIII-20), whose properties will be discussed in Chapter XXI.



(XIII-18)



(XIII-20)



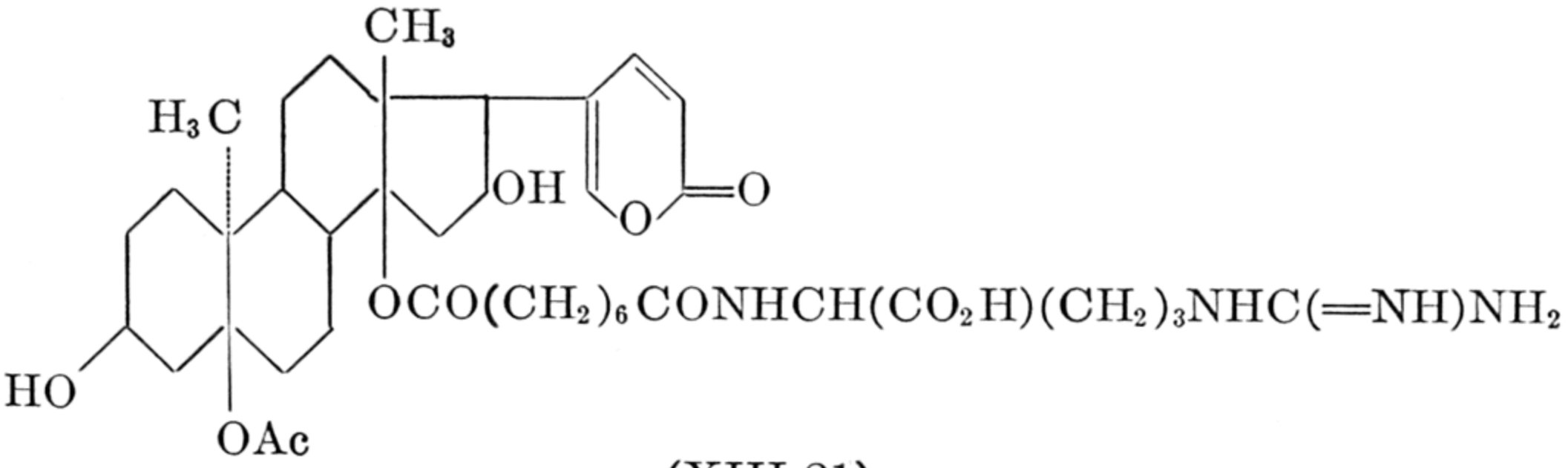
(XIII-19)

[18] See the review articles by Shoppee, *Ann. Rev. Biochem.*, **11,** 135 (1942); and Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, New York, 1949, pp. 560–577.

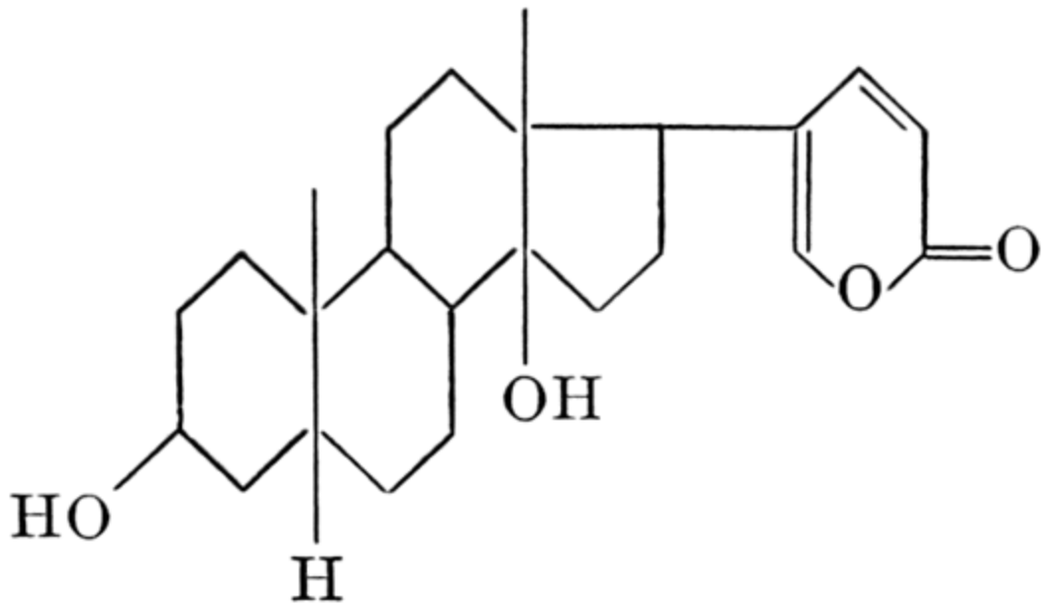
[19] Wieland, Konz, and Mittasch, *Ann.*, **513,** 1 (1934).

The cardiac poisons in toad venom have the same steroid α,β-unsaturated lactone structure which is characteristic of the digitalis genins. In place of sugar components, they contain suberylarginine, $HO_2C(CH_2)_6CONHCH(COOH)(CH_2)_3NHC(=NH)NH_2$, as a conjugating unit.

Only two genins and one conjugate have been adequately characterized. They are bufotaline and its suberylarginine conjugate, bufotoxin, as well as bufalin. The structure of bufotoxin (XIII-21) as accepted now was established by Wieland between 1922 and 1936, that of bufalin (XIII-22) by Meyer.[20] It should be noted that bufalin resembles digitoxigenin structurally and sterically but contains a six-membered lactone ring.



(XIII-21)



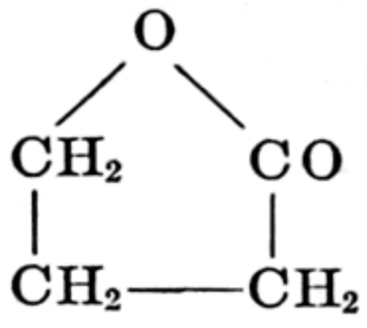
(XIII-22)

4. Structure and Cardiotonic Activity

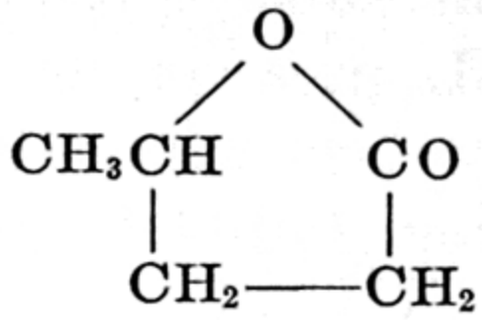
In a series of compounds whose homogeneity and purity has been subject to so much discussion, and whose bioassay rests on methods of questionable value, the values obtained by one investigator and under comparable conditions afford the best means of comparison of their activity. Sixty-three glycosides and genins have been measured by Chen[21] and the following conclusions have been drawn from his figures. This author has expressed the LD_{50} both in mg./kg., and in micromoles/kg.

[20] Kuno Meyer, *Experientia*, **4,** 385 (1948); *Helv. Chim. Acta*, **32,** 1903 (1949).
[21] Chen, *Ann. Rev. Physiol.*, **7,** 681 (1945). Stoll, *J. Pharm. Pharmacol.*, **1,** 849 (1949).

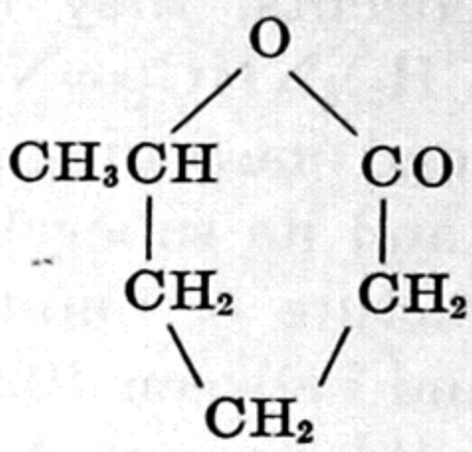
TABLE III. TOXICITY OF VARIOUS LACTONES, PYRONES AND FURAN DERIVATIVES ON THE ISOLATED FROG HEART[22, 23]



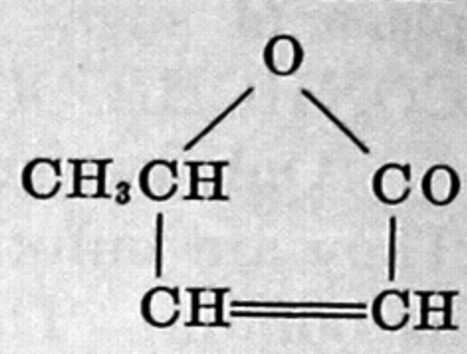
Butyrolactone
10; 498



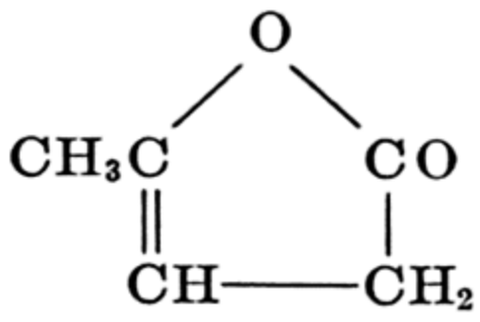
γ-Valerolactone
10; 485



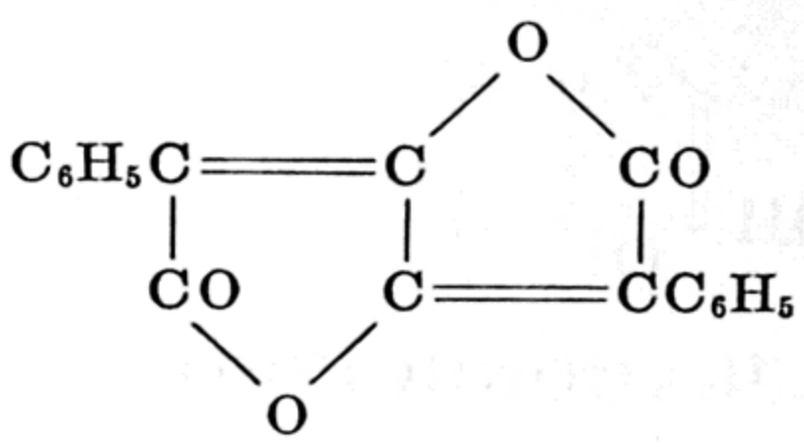
δ-Caprolactone
10; 292



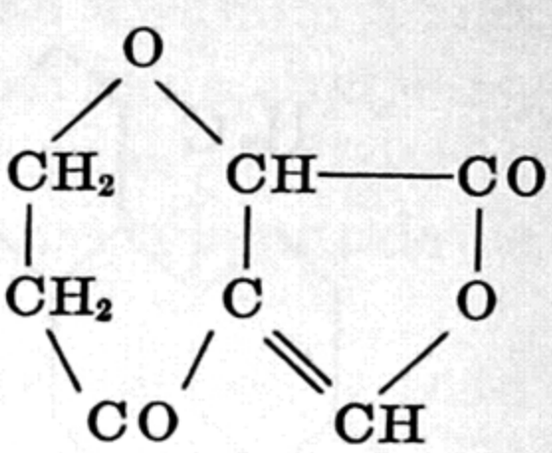
2-Pentene-1,4-olide
10; 68



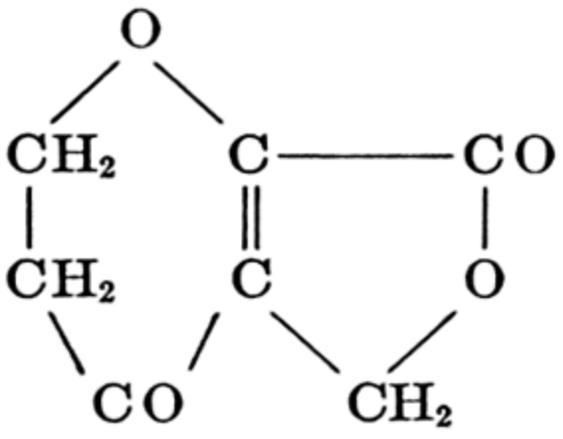
3-Pentene-1,4-olide
10; 18



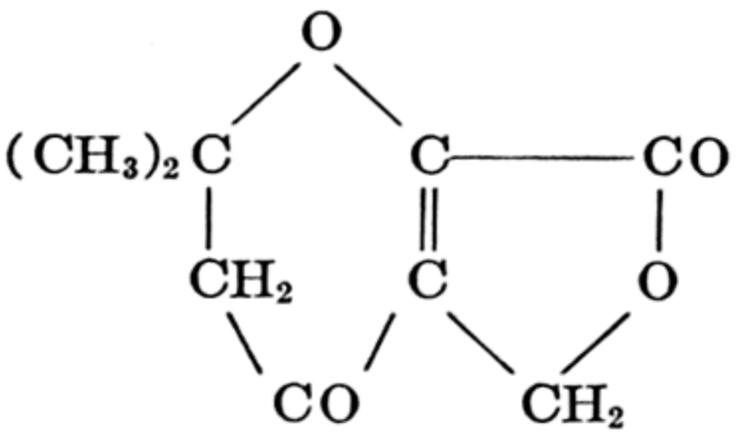
Pulvinic Acid Dilactone
0.4; 15
0.005; 110



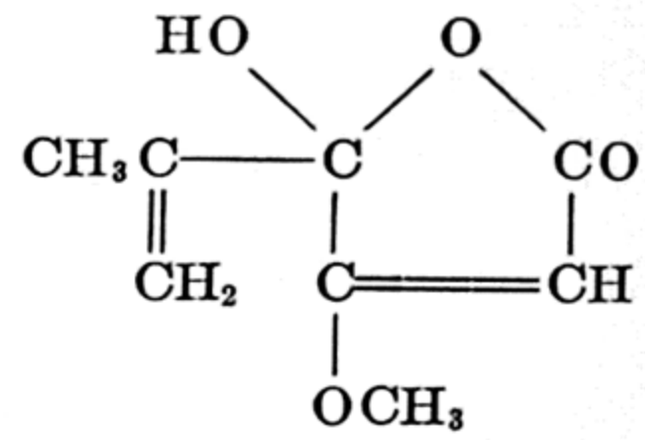
Clavacin
10; 24



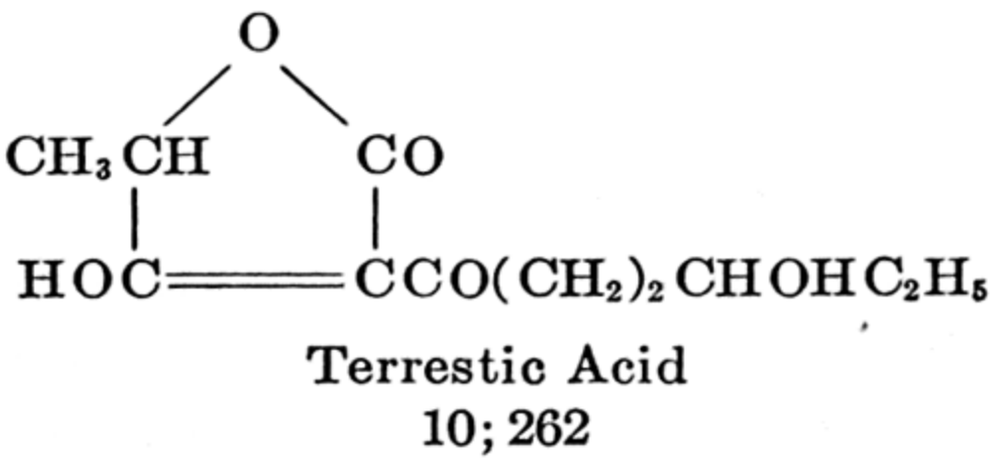
Isoclavacin
10; 10



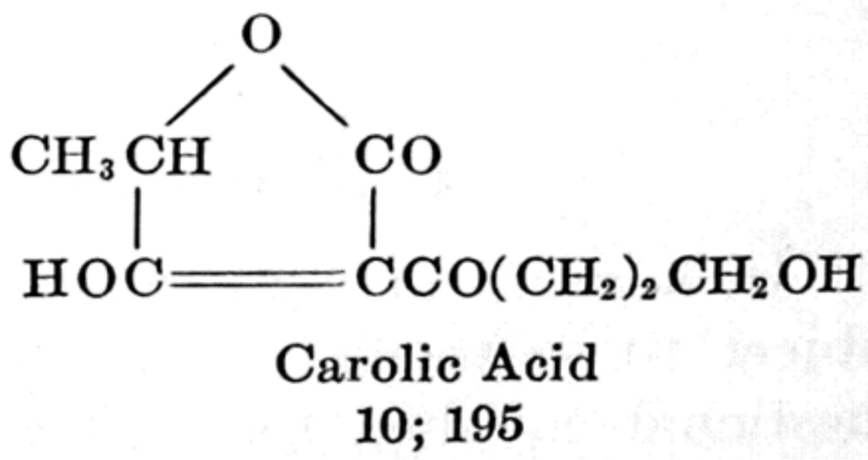
Dimethylisoclavacin
10; 204



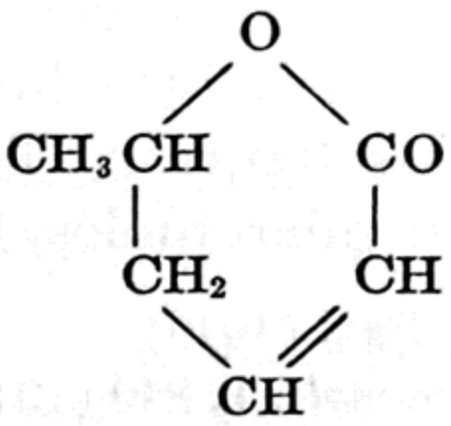
Penicillic Acid
10; 87



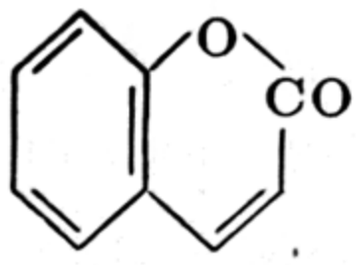
Terrestic Acid
10; 262



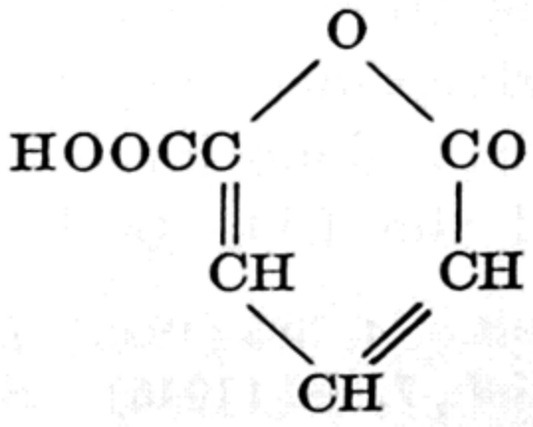
Carolic Acid
10; 195



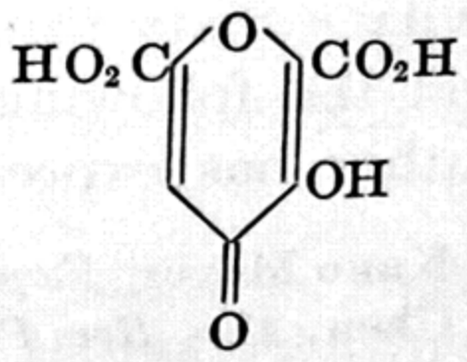
Parasorbic Acid
10; 110



Coumarin
10; 227

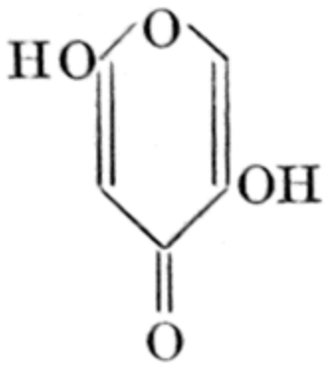
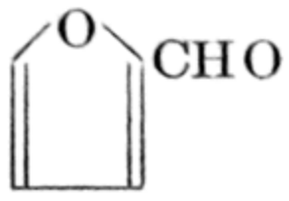
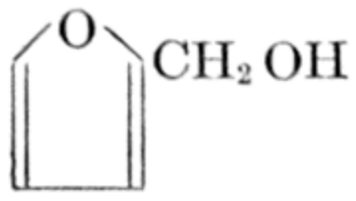
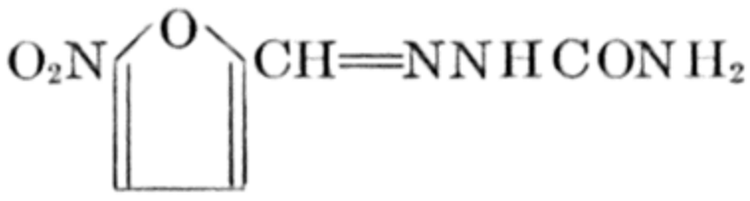


Coumalinic Acid
10; 45



Meconic Acid
10; 30

Table III (*Continued*)

			
Kojic Acid	Furfural	Furfuryl Alcohol	Nitrofurazone
10; 205	10; 165	10; 150	0.8; no standstill after 10 hours

If the latter values are studied, the differences between the individual drugs are less striking than on the mg./kg. scale. Since the compounds are so highly toxic, smaller actual therapeutic doses are of real advantage, and evaluation on this basis may give a better picture of their usefulness.

The glycosides having a 2-desoxysugar component are much harder to hydrolyze than those with a 2-hydroxy saccharide. If rate of hydrolysis to the genin were a decisive factor for cardiotonic activity, the 2-desoxy saccharides would be expected to be less active. This is actually the case in a few instances but no generalizations can be drawn concerning this point. Rhamnose seems to be present in several more active glycosides while the same genins, in conjunction with thevetose, are much less active. In any case, the unconjugated aglycones are on the whole less active than their glycosides. Acetylated aglycones are somewhat more active than the parent secondary alcohols.

Saturation of the α,β-unsaturated lactone rings abolishes activity. There is no marked difference between the activity of glycosides containing butenolide or pentenolide rings. The aldehyde group in strophanthidin can be reduced to $-CH_2OH$ (strophanthidol) without loss of activity but oxidation to carboxyl abolishes it. The stereochemistry of the sterane ring system is apparently of great importance. The lactone group must have the normal sterical relation to the cyclopentane ring. One aglycone having the cis configuration at the A/B ring juncture is about 15 times more active than its stereoisomer (A/B trans).

An extensive study of the cardiotonic properties of fourteen synthetic lactones and several related structures has recently been published.[22] The compounds are represented in Table III.

From these data one can conclude that unsaturated lactones are more active than their saturated analogs, especially if the double bond is in the

[22] Giarman, *J. Pharmacol. Exptl. Therap.*, **94,** 232 (1948); **96,** 119 (1949).

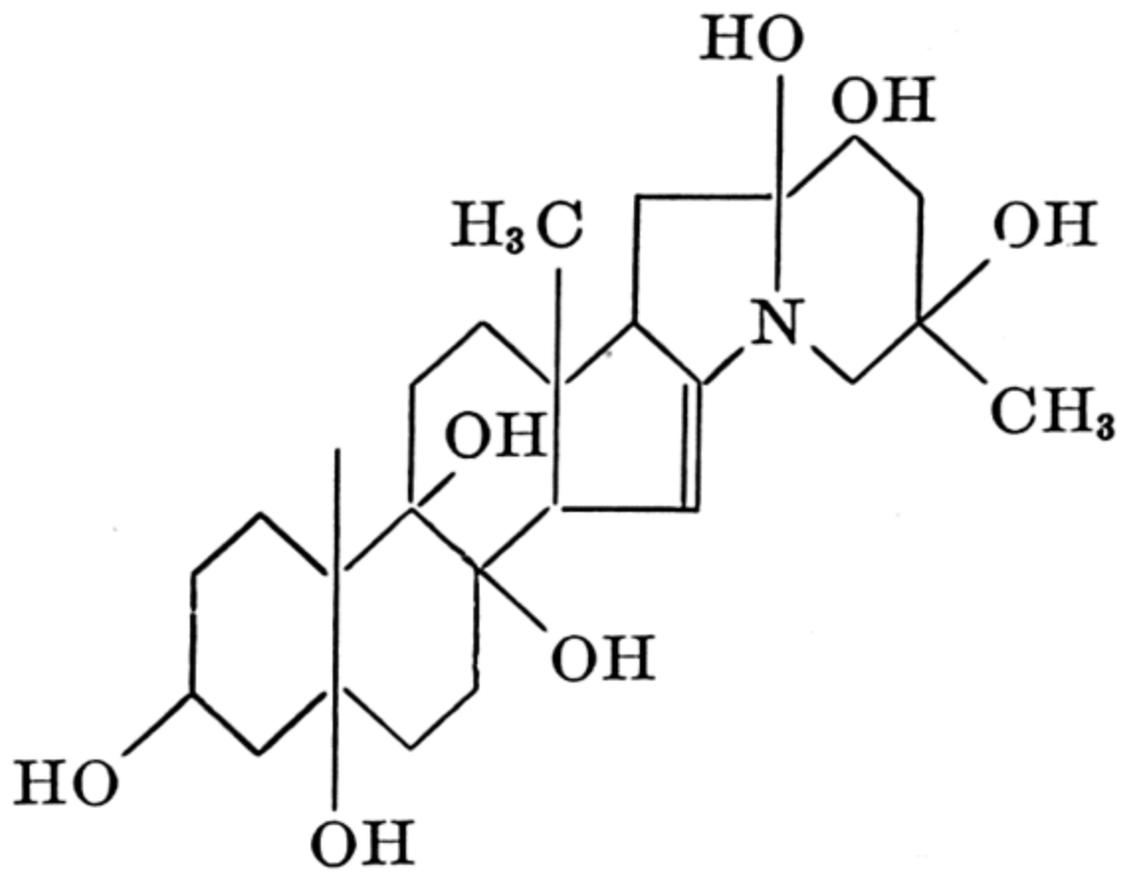
[23] The first figure under the name of each compound represents concentration of mg. in 100 cc. which brings about cardiac arrest in a given time. This time is expressed in minutes in the second figure.

Δ-2 position of the lactone ring. Δ-J-Unsaturated lactones were almost as active, provided their double bond was part of a conjugated system. Alkylation of the lactones decreases activity.

The γ-pyrones which were studied as analogs to lactones showed a high order of activity when containing a conjugated system of double bonds. Furans no longer possessed much cardiotoxicity and failed to induce systolic standstill like the other compounds listed.

II. VERATRINE ALKALOIDS

Interest in the potential therapeutic value of alkaloids from *Veratrum* species has been revived recently through the clinical work of Krayer.[24] These compounds and their derivatives decrease the rate of respiration and have effects on heart and circulation similar to those of the cardiac glycosides. Like the latter, they are conjugates of steroid glycols or hydroxy ketones, but contain a mono- or bicyclic nitrogen ring system in place of the lactone ring. The nature of the heterocyclic system is not quite clear; it has been represented as shown in (XIII-23) for the alkamine cevine.



(XIII-23)

The therapeutic margin of safety of the veratrine alkaloids is low. Only protoveratrine seems to lower blood pressure without nauseating side actions. The conjugates are often ten times more active than the products of hydrolysis, the steroid alkamines.

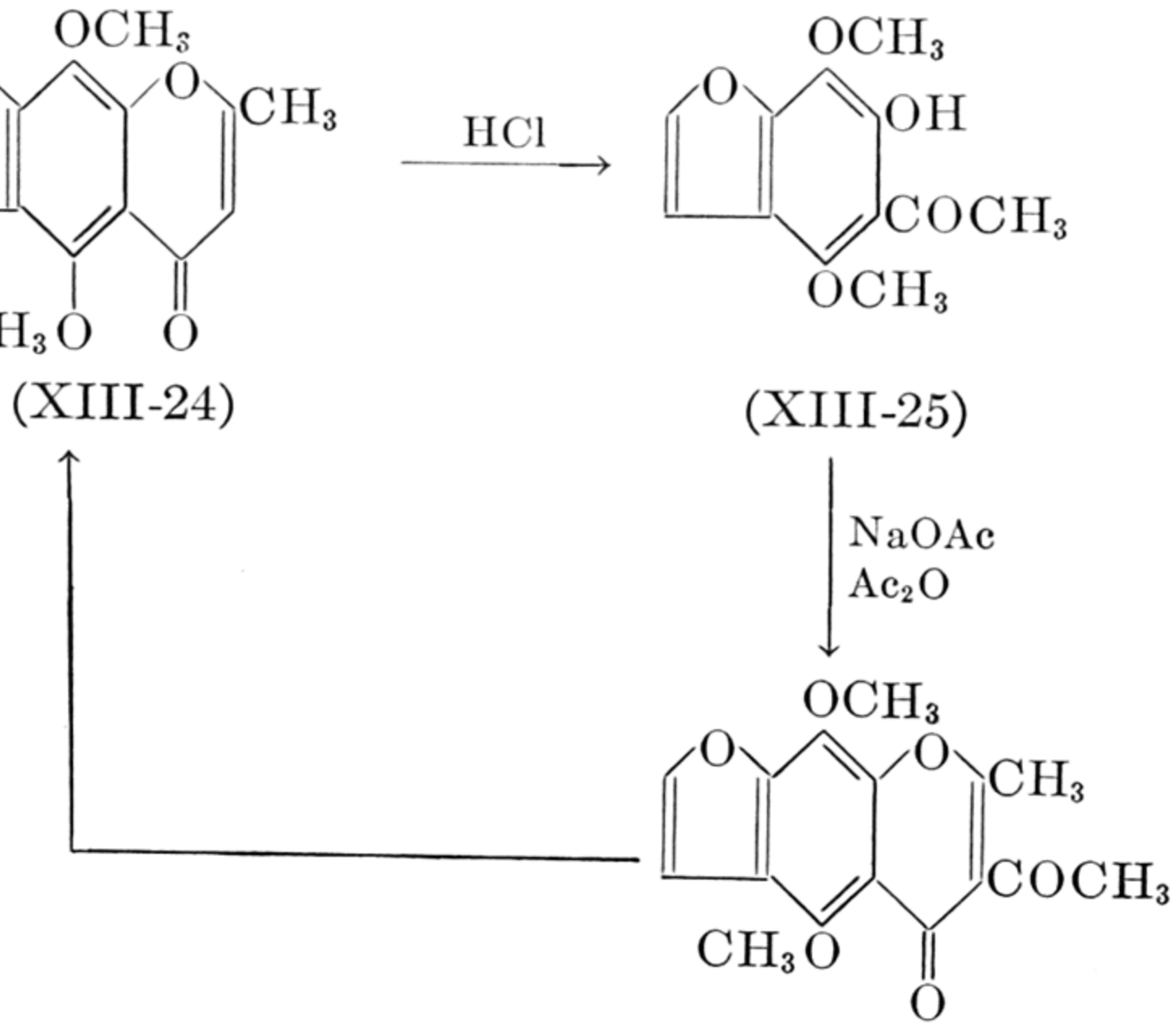
III. KHELLIN AND VISNAGIN

The seeds of the Eastern Mediterraean plant *Ammi Visnaga* contain a number of furanochromone derivatives which have a specific local dilating action on the coronary vessels of the heart in animals and in man. The pharmacological and medicinal observations stem largely from a

[24] Krayer and Acheson, *Physiol. Revs.*, **26,** 383 (1946).

group of Egyptian investigators led by Anrep, Samaan, and Bagouri. Their clinical findings indicate that khellin (also called visammin), and possibly some of the materials accompanying this main constituent in the plant, are powerful coronary vasodilators whose specific action brings relief from the spastic pain of angina pectoris and other heart diseases. In addition, bronchial asthma is also said to be relieved by khellin by relaxation of the bronchial muscles. This affords symptomatic relief in whooping cough.

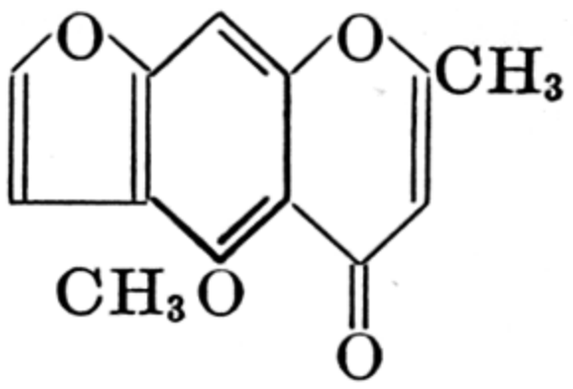
The chemistry of the compounds found in *Ammi Visnaga* was studied by Späth and Gruber[25] who elucidated the structure of khellin (XIII-24) as 2-methyl-5,9-9-dimethoxyfuranochromone by degradation to khellinone (XIII-25). This *o*-hydroxyketone was degraded further to known simpler substances. They also re-synthesized khellin from khellinone by heating with sodium acetate in acetic anhydride medium by a typical chromone ring closure.



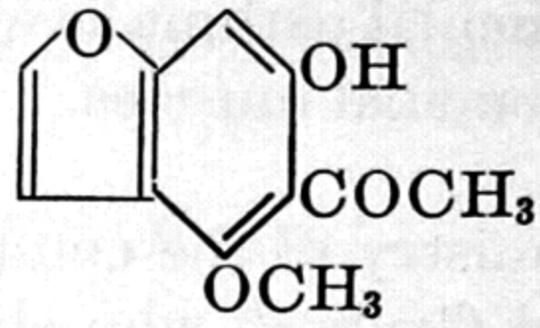
A complete synthesis of khellinone and a more lucid chromone cyclization was carried out by Clarke and Robertson,[26] and the structure was further confirmed by two other syntheses.[27] None of these syntheses is applicable to manufacturing processes, and natural khellin has so far been used by the medical profession.

[25] Späth and Gruber, *Ber.*, **71,** 106, 113 (1938).
[26] Clarke and Robertson, *J. Chem. Soc.*, 302 (1949).
[27] Geissman, *J. Am. Chem. Soc.*, **71,** 1498 (1949). Seshradri, *Proc. Ind. Acad. Sci.*, **A30,** 107 (1949).

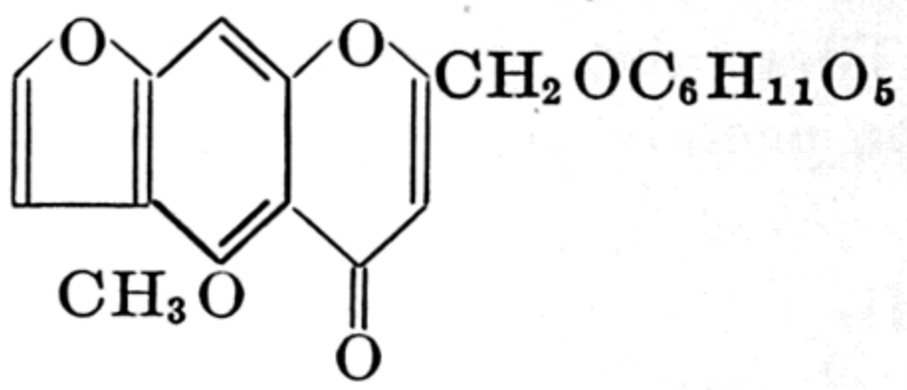
The other materials isolated from the plant are visnagin (2-methyl-5-methoxyfuranochromone, XIII-26) and khellol glucoside (XIII-27). Visnagin can be degraded to visnaginone (XIII-28) in analogy to the dimethoxy series derived from khellin. Khellol-glucoside must be hydrolyzed to khellol and glucose before it can be degraded further.



(XIII-26)



(XIII-28)



(XIII-27)

The relative activities of these compounds in a bio-assay as announced by Anrep, Barsoum and Kenaway are listed in Table IV.

TABLE IV. RELATIVE ACTIVITIES OF CONSTITUENTS OF *Ammi Visnaga* AND RELATED PRODUCTS

Compound	Dose, $\mu\gamma$	% Activity of Khellin	Type of Action: Coronary Dilatation	Type of Action: Intestinal Relaxation	Type of Action: Bronchial Relaxation
Khellin	10	100	active	active	active
Visnagin	15	66	active		
Khellolglucoside	300	trace	inactive	inactive	inactive
Khellinone	30	33			
Visnaginone	50	20			
Khellol	40	25			

In contrast to khellin and visnagin, khellol glucoside exhibits a vasoconstrictive action. One is led to wonder whether oxidation of the 2-methyl group is a means of "detoxifying" the vasodilator activity of visnagin.

IV. THE NITRITES

The nitrite ion (ONO^-) has the ability of relaxing the smooth muscles of the smaller blood vessels independent of innervation. This brings about

vasodilation and a fall in blood pressure. Its effect is most marked in the coronary vessels, and this has established nitrites as invaluable drugs in the relief of pain in angina pectoris. This use overshadows the potentialities of many minor pharmacodynamic actions of the nitrite ion.

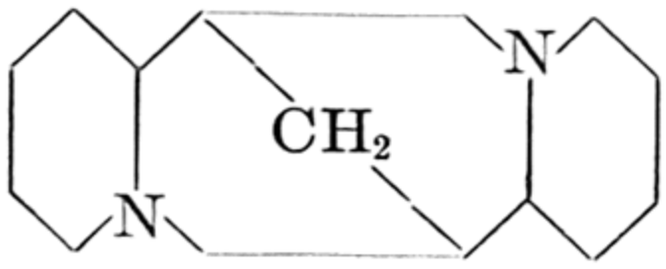
Untoward side effects from the repeated administration of nitrites are methemoglobinemia and other toxic symptoms. Tolerance to nitrites develops readily, and even cross-tolerance to different drugs acting as a source of nitrite ions occurs often.

The most readily available forms of nitrite ions are inorganic nitrites, for example, sodium nitrite. Volatile alkyl nitrites, particularly ethyl and amyl nitrite, are inhaled, absorbed through the lungs and hydrolyzed to nitrous acid in the body fluids. They exert a fleeting action on coronary blood vessels. (2-Ethyl-*n*-hexyl)nitrite has been recommended as a long-lasting vasodepressor of low toxicity.[28]

Nitrite ions do not remain unchanged in the body; they are both oxidized to nitrates, and reduced to ammonia by metabolic reactions. Likewise, alkyl nitrates are a good source of nitrite ions since they are apparently reduced readily. Glycerol trinitrate [$(O_2NOCH_2)_2CHONO_2$], and several polynitrates of carbohydrate-derived hexahydric alcohols are widely used. Among the latter are erythrityl tetranitrate, mannitol hexanitrate, sorbide dinitrate, and isomannide dinitrate. Their structure influences their rates of absorption, reduction and hydrolysis, and thereby their release of nitrous acid. Since a rapid nitrite effect is usually desired in acute attacks of angina pectoris, amyl nitrite and nitroglycerin are preferred for this purpose; they produce nitrite ions more rapidly than other organic esters of nitrous or nitric acid. The higher-molecular polynitrates are suitable as prophylactic agents because they release much nitrite ion slowly and over longer periods of time.

V. SPARTEINE

Mention should be made of the diuretic and cardiac action of the lupinane alkaloid, *l*-sparteine (XIII-28) which has been made use of in medicine.[29]



(XIII-28)

[28] Krantz, Carr, and Forman, *J. Pharmacol. Exptl. Therap.*, **64,** 302 (1938); *Proc. Soc. Exptl. Biol. Med.*, **42,** 472 (1939).

[29] Leonard and Beyler, *J. Am. Chem. Soc.*, **70,** 2298 (1948). Henry, *The Plant Alkaloids*, 4th ed., Blakiston, Philadelphia, 1949, p. 152.

CHAPTER XIV

Parenteral Fluid Therapy

The body of man and mammals consists of about 75 per cent of water. Cellular water comprises up to one-half of the total weight of the organism. This fluid contains potassium, magnesium and phosphate ions and serves as a buffered solvent for water-soluble cell chemicals. The extracellular fluid makes up about one-fourth of the body weight and consists largely of the water in the circulation, the blood and the lymph. It is the solvent of plasma proteins and serves as a vehicle for the transport of blood corpuscles, metabolites and waste products. In addition to plasma-water, extracellular water fills the spaces between tissues. It contains sodium chloride, calcium, potassium, and phosphate ions.

The volume of plasma is fairly constant except in bleeding or burns, and any dehydration of the body occurs mainly at the expense of extracellular water between the tissues (one-fifth of the body weight.) Normal losses of water proceed by way of moist air exhaled from the lungs, through the perspiration, and by excretion through the kidney. Severe alterations of the water volume of the body are caused by diarrhea, vomiting, as well as by hemorrhages and burns. In these conditions, fluids may have to be infused parenterally into the organism in order to prevent dangerous dehydration and the accompanying concentration of solutes.

Retention of water is caused by inefficient ("compensating") kidneys. If dehydration and compensating kidneys are present together, even erythrocytes may appear in the urine.

I. SALT SOLUTIONS

The solutions most frequently employed to replace bodily fluid are dextrose (5%), salt (0.9%, normal saline), Ringer's solution (NaCl, 0.85%; KCl, 0.03%; $CaCl_2$, 0.03%), lactate Ringer's solution, sodium rac.-lactate (1.87%), glucose and sucrose (50%), and amino acids or protein hydrolysates.

The most urgent need for parenteral fluid therapy is in traumatic shock. The first consequences of heavy loss of blood are the immediate decrease of the circulation. Even if as much as one-third to one-half of the total blood is shed, the collapse of the circulatory system is caused largely by the inability of the remaining blood supply to fill the vessels.

Only in even heavier acute losses of blood, the loss of erythrocytes will impair the transport of oxygen to the vasomotoric and respiratory centers. It is therefore imperative to replace immediately the lost volume of liquid by intravenous infusion.

Physiological salt solutions are of definite value for this purpose, and are well tolerated. However, their effect wears off rapidly, since they are eliminated by the kidney and by the sweat glands in about two hours. If the liquid volume of the circulation is to be maintained for many hours or even days, suitable hydrophilic colloids must be added to the salt solutions. The molecular size of the colloid must be sufficient to prevent the material from permeating the damaged walls of the blood vessels, and the colloid must be free from sensitizing allergenic properties.

II. POLYVINYLPYRROLIDONE

The first macromolecular compound which fulfilled these requirements satisfactorily was the polyvinylpyrrolidone (XIV-1) synthesized by Reppe during the war.[1] A 3.5% solution of this material ("Kollidon") containing 0.9% of sodium chloride, 0.042% of potassium chloride, 0.025% of calcium chloride, 0.0005% of magnesium chloride, and 0.0024% of sodium bicarbonate as well as about 10 volume-per cent of free CO_2 is isotonic and has pH 6.0. Its viscosity is 3.0; it can be sterilized by heating and kept interminably. The molecular size of the colloidal constituent is 25,000. This solution has been marketed under the name of Periston.

It is obvious that Periston can only substitute for the hemodynamic functions of blood. It cannot contribute to oxygen transport, coagulation time, defense mechanisms and other chemical and biological functions of whole blood. However, it can serve as a stop-gap between the time of injury and the first opportunity to secure a blood transfusion, and the solution has fulfilled this mission during World War II in many instances.

Peristone raises blood pressure to normal levels after severe bleeding and does not interfere with diuresis and liver functions. It has been used successfully in cases of systemic dehydration due to diarrhea or vomiting.

The synthesis of polyvinylpyrrolidone, although a six-step process, is inexpensive and adaptable to manufacturing conditions. Formaldehyde is added to acetylene, and the resulting butyne-2-diol-1,4 (XIV-2) is hydrogenated to butane-diol-1,4 (XIV-3). Catalytic dehydrogenation of this glycol furnishes γ-butyrolactone (XIV-4) which yields the lactam (α-pyrrolidone, XIV-5) on heating with ammonia. The amide hydrogen atom can be replaced by the vinyl group, and N-vinyl-α-pyrrolidone

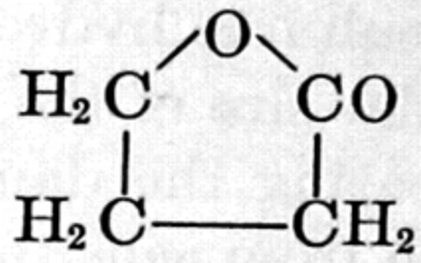
[1] British Intelligence Objectives Sub-Committee, Final Report No. 354, Item No. 22, H. M. Stationery Office, London, 1945.

(XIV-6) thus obtained is polymerized under the catalytic influence of hydrogen peroxide at 180–190°. The polymer (XIV-1) is soluble in water and most organic solvents. The aqueous solutions are neutral and behave, on the whole, like solutions of albumin.

$$2HCHO + HC{\equiv}CH \xrightarrow[1\%\ \text{Cu-acetylide}]{80\text{–}100^\circ,\ 100\ \text{atm.}} HOCH_2C{\equiv}CCH_2OH \rightarrow$$

(XIV-2)

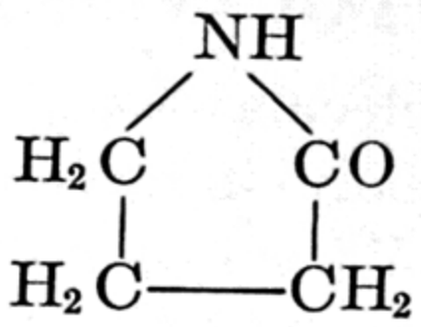
$$\xrightarrow[100\ \text{atm.}]{H_2,\ Ni,\ 200^\circ} HO(CH_2)_4OH \xrightarrow[170\text{–}180\ \text{atm}]{Cr\text{–}Ni,\ 200^\circ}$$



(XIV-4)

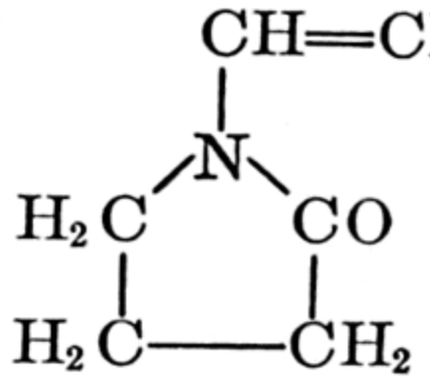
(XIV-3)

$$\xrightarrow[100\text{–}200\ \text{atm.}]{NH_3,\ 230^\circ}$$



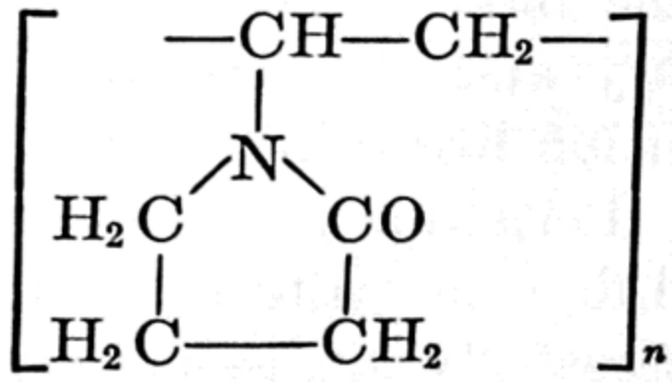
(XIV-5)

$$\xrightarrow[10\text{–}20\ \text{atm.}]{HC{\equiv}CH,\ KOH,\ 140\text{–}160^\circ}$$



(XIV-6)

$$\xrightarrow[180\text{–}190^\circ]{30\text{–}40\%\ H_2O_2}$$



(XIV-1)

III. POLYVINYLPYRROLIDONE AS RETARDING VEHICLE[2]

Polyvinylpyrrolidone has been studied extensively as a retarding vehicle for insulin and other hormones, for antibiotics, local anesthetics and other functional drugs. The colloid slows down the diffusion of these materials and thereby prolongs their effect. Insulin—P.V.P. is at least as long-acting as zinc-protamin-insulin, and produces up to 50% longer a

[2] Durel, *J. des Practiciens*, **62,** 273 (1948).

duration of hypoglycemic effects than insulin alone. The circulation time of penicillin is doubled by simultaneous intravenous administration of polyvinylpyrrolidone. Novocaine lasts longer in the circulation and in various tissues, including nerve ganglia where it can be used for prolonged anesthesia in peripheral diseases. The effects of sodium salicylate, of the antihistaminic drug Phenergan, of the vasodilatory tetraethylammonium bromide, and of mercurial diuretics are equally affected by polyvinylpyrrolidone. In certain cases, co-injection of the colloid has made possible a practical application of an otherwise rapidly disappearing drug.

IV. DEXTRAN

In refining beet sugar, the organism, *Leuconostoc mesenteroides* often contaminates the sugar solutions. This organism has the ability to polymerize glucose to polysaccharides of very high molecular weights, and under controlled conditions a product can be prepared which after hydrolysis has a molecular weight of 100,000, comparable to that of plasma proteins. It has been tested under the name of Dextran and has been found to give favorable results in experimental and clinical shock. It may be that the polymer is hydrolyzed to glucose in the body and thereby fulfills both a role as a colloidal adsorbing and of a nutritional agent.[3]

[3] Holland, *Am. J. Pharm.*, **121,** 449 (1949).

CHAPTER XV

Diuretics

Diuretics are chemicals which alter renal function in a clinically useful manner by promoting the formation of urine, and thereby aid in the elimination of excess liquid and toxic products from the tissues and circulation.

Urine is produced in the kidney by a complex multiple ultrafiltration of the blood serum. The capillary bed of the kidney, the glomerulus, is one of the factors of urine formation. The other filter apparatus are the renal tubuli which concentrate the glomerular filtrate by reabsorption, and excrete the urine to the bladder. A detailed account of the physiological functions of the kidney can be found in any text of pharmacology or physiology, and an understanding of the forces which bring about diuresis should be of value to medicinal chemists interested in this field.[1]

Broadly speaking, two types of diuretics can be distinguished. The first group includes simple substances such as water, alkali chlorides, ammonium and calcium halides and nitrates, urea, glucose and sucrose which alter the osmotic pressure of the serum and thereby promote diffusion through the glomerular and tubular membranes. The resulting changes of osmotic conditions are complicated and not clearly understood for all the diuretics named. The possibility is not excluded that some, if not all, of these compounds produce their effects by enzymatic as well as osmotic mechanisms.

The second group of diuretics is of greater interest to medicinal chemists. In this group are found mercurials, the xanthines theobromine and theophylline, digitalis aglucones, and hormones, especially of thyroid and parathyroid origin. These drugs act as inhibitors or as positive catalysts of kidney enzymes which control diuresis by intermittent phosphorylation and other reversible reactions of serum constituents.

I. UREA AND UREA DERIVATIVES

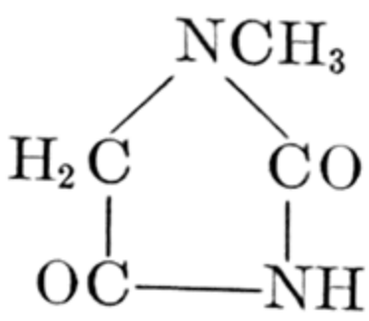
The diuretic activity of urea was discovered accidentally when it was administered experimentally in the treatment of kidney stones; it appeared possible that it could dissolve uric acid granules. In spite of its disagree-

[1] cf. Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, Macmillan, New York, 1941, p. 627.

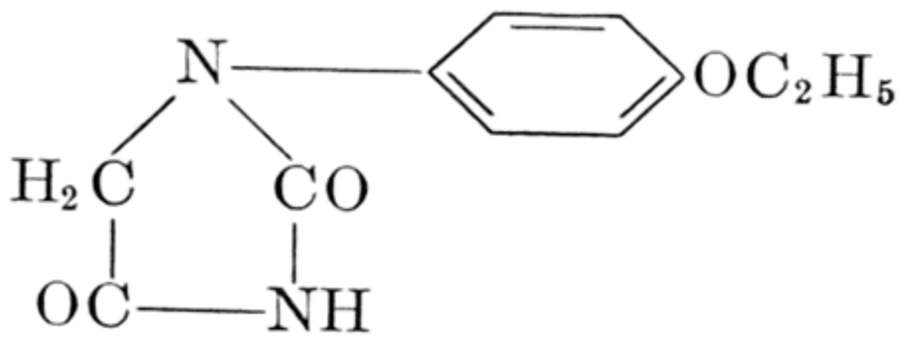
able taste and the large amounts necessary to produce diuresis, urea has remained a valuable drug and is regarded by many clinicians as the most effective non-metallic diuretic agent in diseases of the liver and the kidney and in cardiac edema.[2]

Urea is the diamide of carbonic acid, and many other amides, urethans, alkyl- and arylureas as well as ureides have been tested as diuretics. Dimethylurea [$CO(NHCH_3)_2$] and di-(*p*-hydroxyethylphenyl)urea [$CO(NH\text{-}p\text{-}C_6H_4CH_2CH_2OH)_2$] are two to ten times more active than urea, and their molar concentrations which increase diuresis are so low that their effect can hardly depend on significant osmotic changes in the kidney. Urea undoubtedly acts, at least in part, by an osmotic mechanism, and substitution thus changes its qualitative diuretic effect. It is possible that this impression is evoked solely by differences in absorption and distribution between the individual urea derivatives, but increases of direct effects on the enzymes controlling filtration and reabsorption in the kidney are the more likely explanation. An increase of iron excretion during the simultaneous administration of urea and ferrous salts points in the same direction. Another explanation is based on the diuretic activity of urethan ($C_2H_5OCONH_2$) which is partly ammonolyzed to urea and ethanol in the organism. In addition, many poorly soluble substances form soluble addition complexes with urethan and can thereby be excreted more readily. These ideas have been applied to other urea derivatives on various occasions.

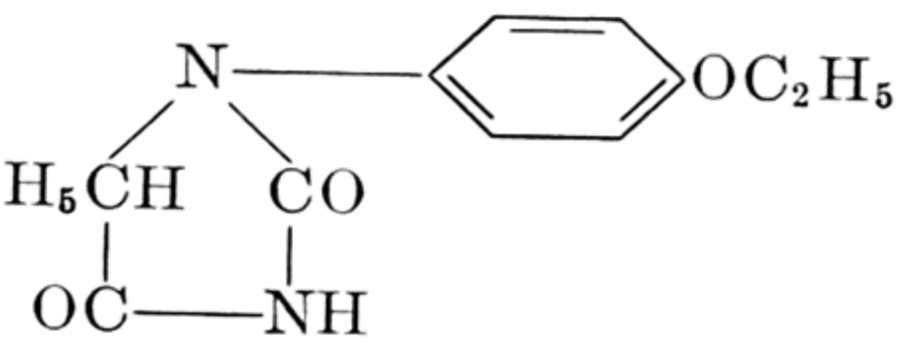
Among the cyclic ureides, N-alkyl- and -arylhydantoins exhibit pronounced diuretic activity. 1-Methylhydantoin (XV-1) causes a greater



(XV-1)



(XV-2)



(XV-3)

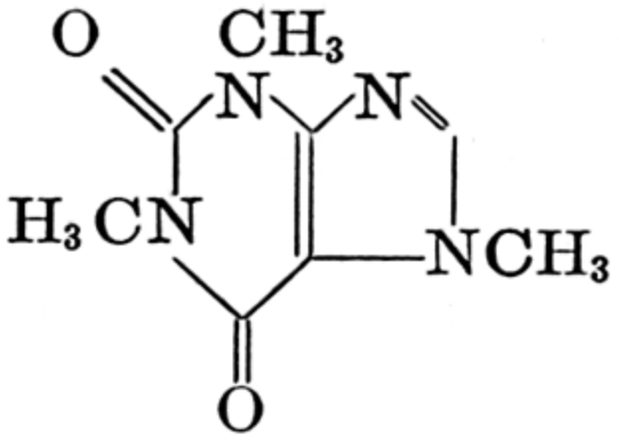
flow of urine than twice the dose of urea, and this result is achieved within a very short period of time, while most other ureides act only after a lapse of several hours. The compound is non-irritating, is quite stable and not

[2] Haas, *Die Pharmazie*, **3,** 97 (1948).

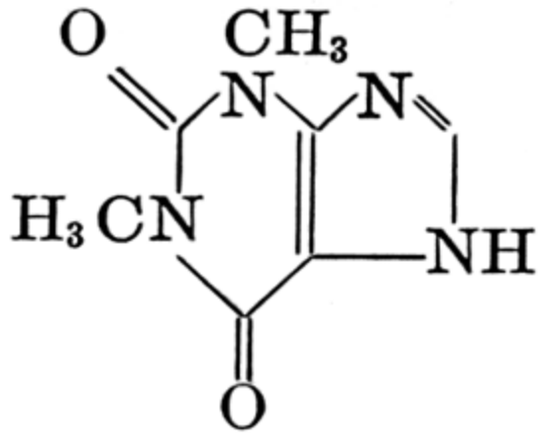
demethylated in the body.[3] 1-*p*-Ethoxyphenylhydantoin (XV-2) and its 5-ethyl derivative (XV-3) possess even greater diuretic properties but their effective doses are close to the toxic ones. Nevertheless, the relationship of these compounds to the anticonvulsant 5,5-disubstituted hydantoins (Chapter X) is suggestive of a central nervous system relation of diuretic and anticonvulsant pharmacology, especially since disturbances of water metabolism seem to play a role in precipitating epileptic attacks.[4]

II. PURINE DERIVATIVES

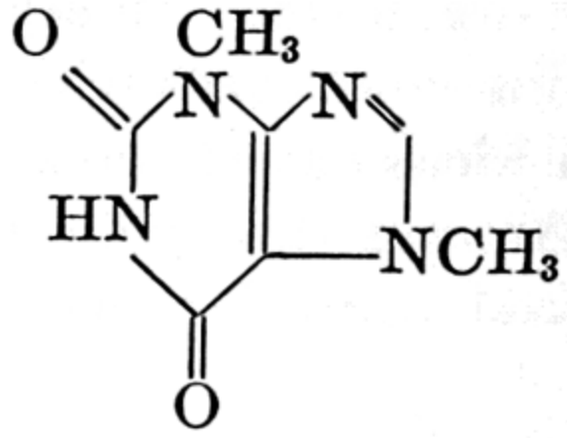
The diuretic properties of the purine derivative, caffeine (XV-4), the alkaloid from tea leaves and coffee beans, were observed over sixty years ago, and those of theophylline (XV-5) shortly thereafter.[5] The latter is almost three times as potent as caffeine, with theobromine (XV-6) occupying an intermediary position. Caffeine is not used clinically because its useful diuretic activity in man is negligible, and is overshadowed by its centrally stimulatory effects. Theophylline and theobromine can be given orally but cause gastric irritation. They are still used occasionally in cardiac edema but not in conditions in which kidney functions have been seriously impaired.



(XV-4)



(XV-5)



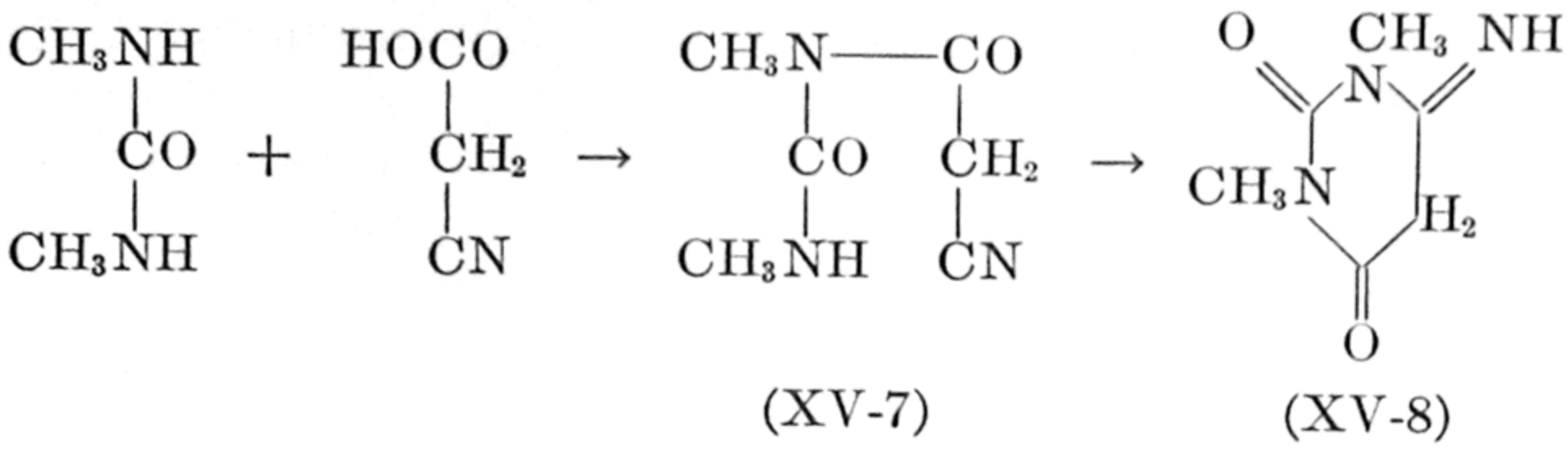
(XV-6)

1. Theophylline

a. Manufacture

The extraction of the naturally occurring theophylline from tea is a very expensive process, and the drug is manufactured primarily by the method of Traube.[6] Condensation of sym.-dimethylurea with cyanoacetic acid under the influence of phosphorus oxychloride yields cyanoacetyl-N,N′-dimethylurea (XV-7) which is cyclized to 1,3-dimethyl-2,6-dioxy-4-aminopyrimidine (XV-8). The isonitroso derivative of this base (XV-9) is reduced to the diamine (XV-10) by means of ammonium sulfide, and the

[3] Gäbler, *J. biol. Chem.*, **67,** 55 (1926); **70,** 763 (1926).
[4] Haas, *Die Pharmazie*, **3,** 97 (1948), refs. 28–32.
[5] Schröder, *Naunyn–Schmiedeberg's Arch. exptl. Path. Pharmakol.*, **24,** 85 (1888). Minkowski, *Therap. Gegenwart*, **1902,** 490.
[6] Traube, *Ber.*, **33,** 3035 (1900).



(XV-7)

(XV-8)

(XV-9)

(XV-10)

(XV-11)

(XV-5)

(XV-12)

(XV-13)

(XV-14)

(XV-15)

(XV-4)

(XV-16)

(XV-5)

formyl derivative of the diamine (XV-11) is converted to theophylline on heating with alkali.

Another industrial synthesis of theophylline starts with uric acid (XV-12) which, on treatment with acetic anhydride, yields 8-methylxanthine (XV-13). Methylation of this intermediate leads to 1,3,7,8-tetramethylxanthine (XV-14). This can be chlorinated to a mixture of 1,3,7-trimethyl-8-trichloromethylxanthine (XV-15) and 1,3-dimethyl-7-chloromethyl-8-trichloromethylxanthine (XV-16) which is separated by fractional crystallization. The trichloro derivative (XV-15) gives up its chlorinated group and yields caffeine (XV-4) while the tetrachloro compound (XV-16) loses both its chlorinated groups and furnishes theophylline (XV-5).[7]

b. Application

Theophylline is applied in the form of double compounds which solubilize the active component. Theophylline-sodium salicylate is known as Diuretin; the sodium acetate double salt as Agurin, and the calcium salicylate double compound as Theocalcin.

The most widely used pharmaceutical preparation of theophylline is a molecular mixture of this reagent with ethylenediamine which has become known as aminophylline. It exhibits good solubility and a favorable therapeutic index. Its usefulness is not restricted to increases of diuresis. It raises blood pressure, counteracts histamine spasm, and is widely employed as an antiasthmatic agent (Chapter XXIV).

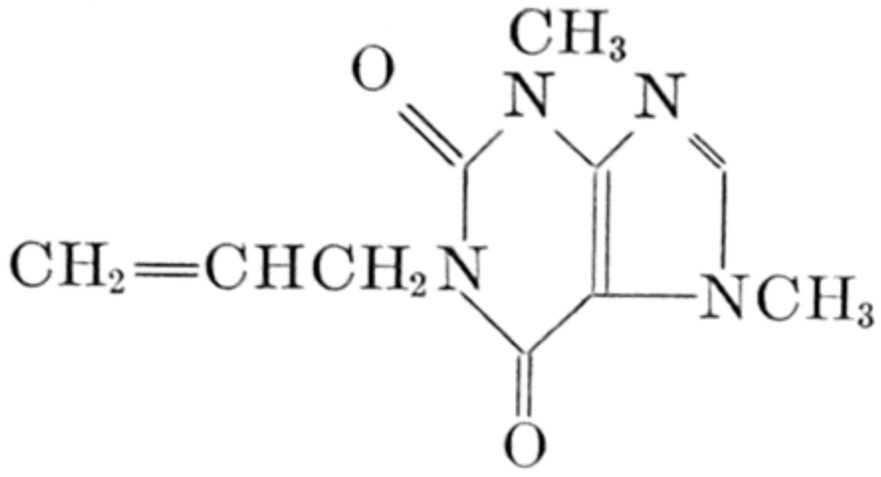
2. Other Purines

Structural alterations of 2,6-dioxypurines (xanthines), such as the replacement of the methyl groups by other small alkyl radicals, or N^1-substitution with groups up to four carbon atoms have not furnished any drug even more effective than caffeine. Only 1-allyl-3,7-dimethylxanthine (XV-17) surpasses theobromine in diuretic activity.[8] Alkoxycaffeines are almost inactive.

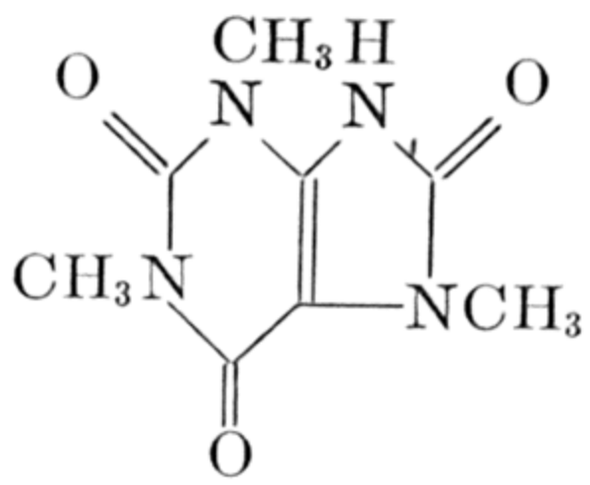
Uric acid (XV-12) acts diuretically, and some of its methyl derivatives show an increased activity. 1,3,7-Trimethyluric acid (XV-18) is quite active and is excreted unchanged. This property has been correlated with diuretic activity in general under the assumption that the unchanged drugs themselves must be active; if they were degraded to the same, or very similar active products *in vivo*, the wide variations in activity between individual xanthines would become hard to explain.

[7] Ullmann, *Enzyklopädie der technischen Chemie*, Vol. 8. Urban & Schwarzenberg, Berlin, 1931, p. 571.

[8] Bergell and Richter, *Z. exp. Ther.*, **1**, 655 (1905).



(XV-17)



(XV-18)

The diuretic properties of theobromine have not been rivalled either by both natural and synthetic nucleosides and nucleotides containing different purine groups. It is possible that colloidal factors play a role in the mechanism of action of these high-molecular compounds. This certainly holds in the case of acacia which contains polysaccharides capable of restoring normal osmotic pressure in nephrotic edema. The polysaccharides apparently substitute for lost serum protein and thereby mobilize the edematic fluid.

The physiological mechanism of the diuretic action of the xanthines is apparently connected with the dilation of the glomerular vessels by these drugs, but central excitation and interference with enzymes catalyzing filtration and reabsorption have also been claimed to influence their mode of action.

III. MERCURIAL DIURETICS

One of the most important applications of organic mercurials is in the production of diuresis. Inorganic salts, notably calomel, have been used as additive and potentiating agents of digitalis diuretics.

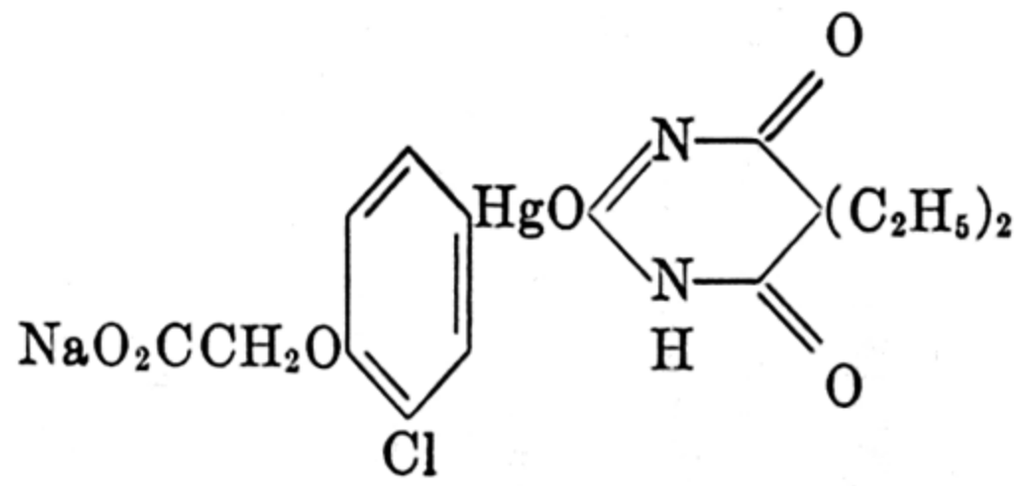
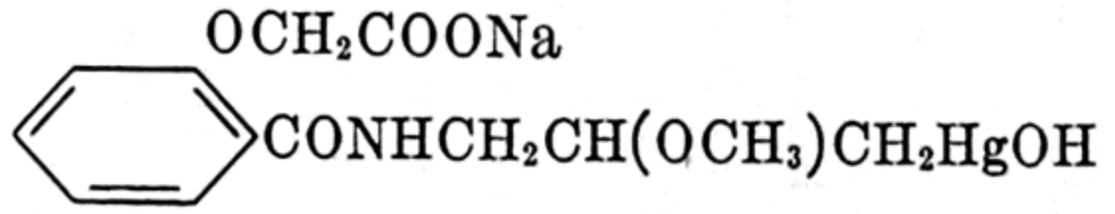
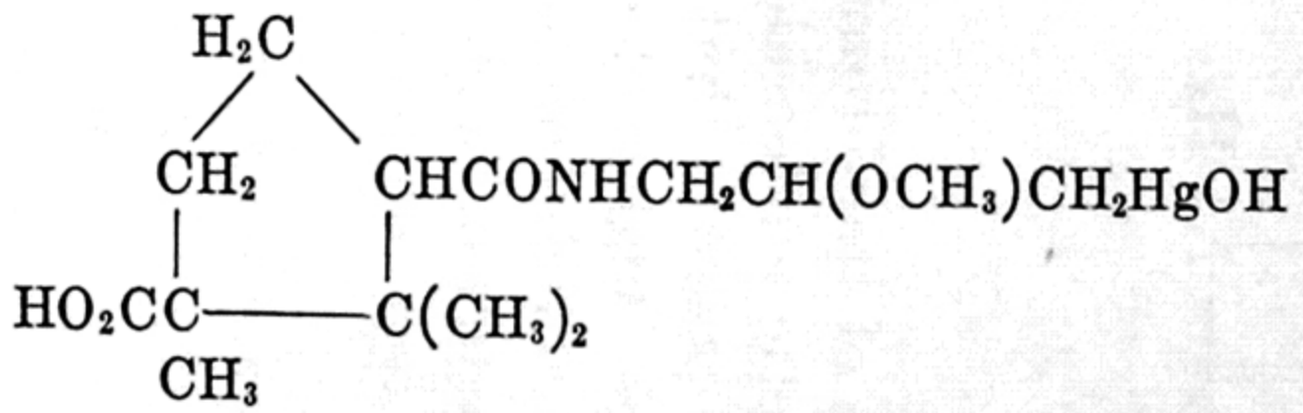
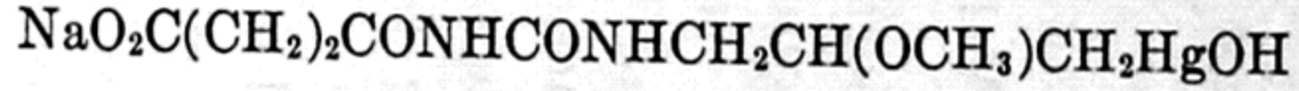
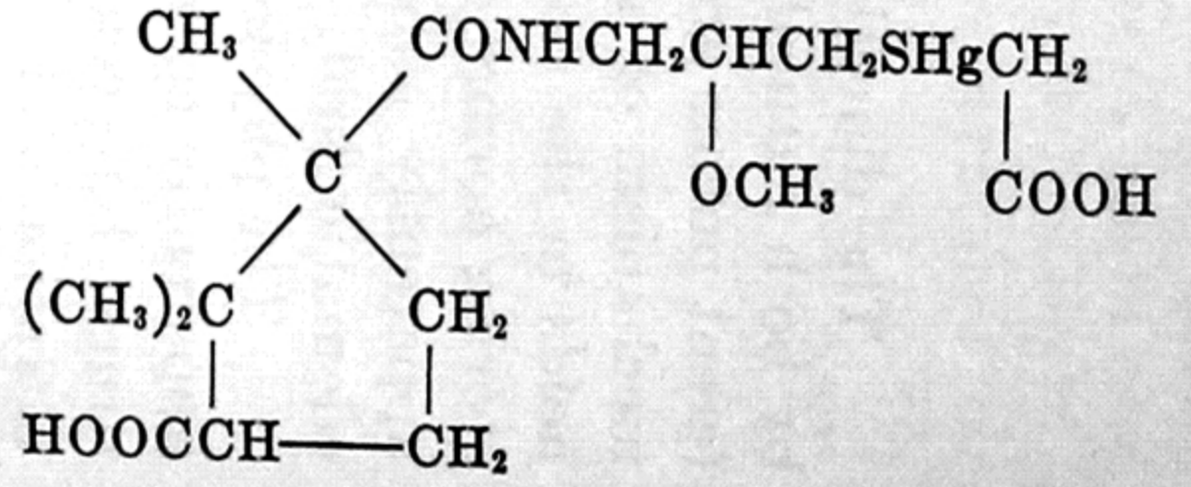
Mercurial diuretics reduce the extracellular fluid compartment, particularly in congestive heart failure (cardiac edema). In this condition, sodium chloride, and thereby water are retained. This is due to the low rate of cardiac output—reduced flow of blood—which diminishes the rate of glomerulal filtration in the kidney. So little sodium chloride is thereby presented to the kidney tubules that all of it is reabsorbed, and barely any salt is excreted. Excretion is increased by diuretics, and excess body weight caused by accumulation of the fluid is reduced rapidly. Edema caused by other conditions, such as tumors, cirrhosis of the liver, thrombophlebitis etc. is often relieved by mercurials.

The accumulation of sodium ions has been combatted occasionally by oral administration of ion-exchange resins but adequately selective materials which do not remove other cations as well are still being sought.[9]

Mercurous chloride, introduced in 1885,[10] is still used extensively but

[9] Ray and Burch, *Am. J. Med.*, **217,** 96 (1949).
[10] Jendrassik, *Deut. Arch. Klin. Med.*, **38,** 499 (1885).

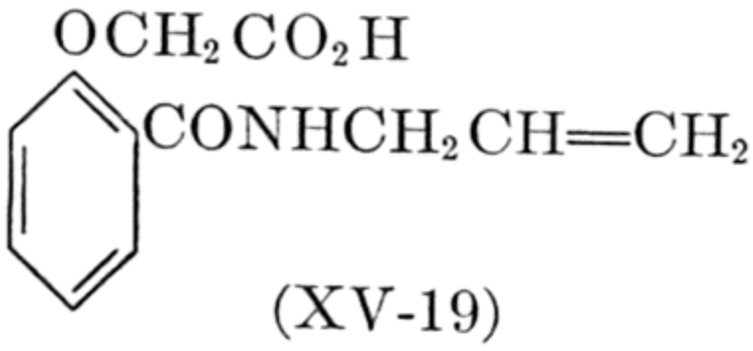
TABLE I. MERCURIAL DIURETICS

Common Name	Chemical Name	Structural Formula
Merbaphen (Novasurol)	Sodium mercurichlorophenyl oxyacetate diethylbarbiturate	
Mersalyl (Salyrgan)	Sodium [*o*-(3-hydroxymercuri-2-methoxypropylcarbamyl) phenoxy]acetate	
Mercurin (Mercupurine is the theophylline salt)	2,2,3-trimethylcyclopentane-1,2-dicarboxylic acid-(3-mercuri-2-methoxypropyl) amide	
Mercuhydrin (as the theophylline salt)	Sodium 3-hydroxymercuri-2-methoxypropyl succinyl urea	
Thiomerin	N-(γ-Carboxymethylmercaptomercuri-β-methoxy) propyl camphoramic acid	

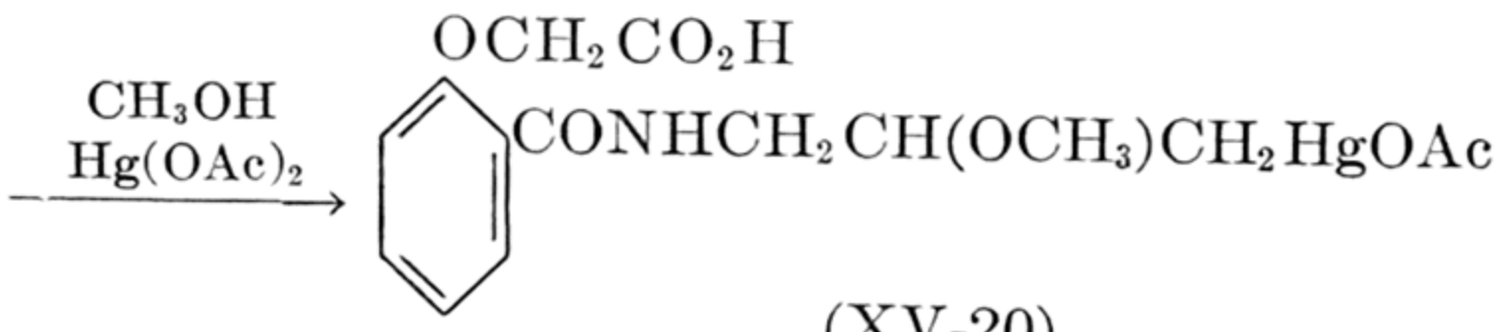
has been rivalled by less toxic compounds having mercury in organic linkage. The most common organic mercurial drugs now in clinical use are listed in Table I. Several of them are marketed as soluble salts of theophylline, the mercury being attached to N-7.

Merbaphen (Novasurol) was introduced originally as an antisyphilitic[11] agent. The diuretic application of this mercurial was discovered only later. This sequence of events characterizes work in this whole group although several recent investigators have searched primarily for diuretics among mercurials.[12] Because this book arranges drugs according to their use mainly, a number of mercurials which act primarily as antiseptics will be discussed in Chapter XXXXIII.

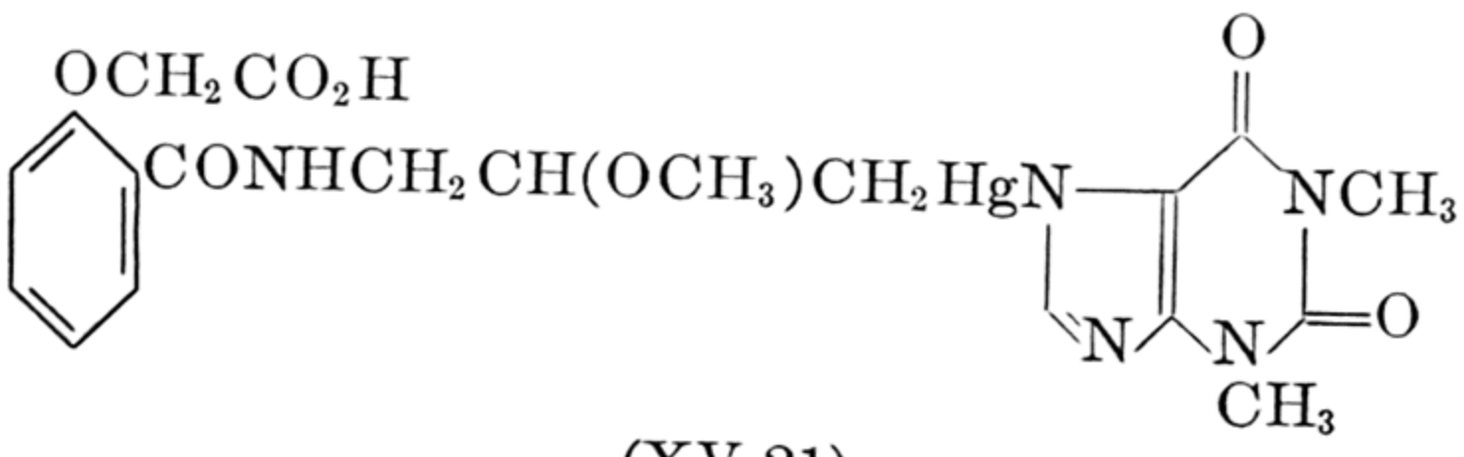
The preparation of Mersalyl may serve as an example of a synthesis of those mercurials which contain the metal atom in the aliphatic side chain. The allylamide of *o*-carboxyphenoxyacetic acid (XV-19) is treated with mercuric acetate in methanol solution; the resulting mercurial (XV-20) is then converted to the salt (XV-21) of a compound containing an acidic nitrogen atom, such as succinimide or theophylline (XV-5).



(XV-19)



(XV-20)



(XV-21)

Starting with allylurea (XV-22) instead of an allylamide, similar derivatives can be elaborated (XV-23).

[11] Saxl and Heilig, *Wien. Klin. Wochschr.*, **43,** 943 (1920). Newman, *Bull. Johns Hopkins Hosp.*, **81,** 430 (1947).

[12] Perry, Foreman, and Friedman, *Abstracts*, 116th Meeting, Am. Chem. Soc., Atlantic City, N. J., September 18–23, 1949, p. 156. Rowland, Perry, Foreman and Friedman, *J. Am. Chem. Soc.*, **72,** 3595 (1950).

$$\underset{\text{(XV-22)}}{H_2NCONHCH_2CH{=}CH_2} + Hg(OAc)_2 + CH_3OH \rightarrow AcOH + \underset{\text{(XV-23)}}{H_2NCONHCH_2CH(OCH_3)CH_2HgOAc}$$

The mercuriacetates can be converted to the more soluble chloromercuri compounds with sodium chloride ($RHgOAc + NaCl \rightarrow RHgCl + NaOAc$).

By using other alcohols in the reaction, a series of alkoxy derivatives can be obtained from allylurea. Some of these compounds produce in dogs diuresis four to five times as great as any of the clinically used mercurial diuretics. The thioacetate ethers ($H_2NCONHCH_2CHORCH_2HgSCH_2COOH$) are distinguished by low systemic toxicity and a greatly reduced rate of irritation when administered subcutaneously.

In Thiomerin, which contains mercaptoacetic acid as an extender of the diuretic action of the mercurial component, cardiac and local toxicity has been reduced to a point where subcutaneous administration is possible.[13]

Several of these organic mercurials contain approximately the same percentage of mercury, namely, about 37–42%. It is believed that their mercury atom becomes ionized, and that the release of organo-mercuri ions depends on the firmness of the organic linkage of the metal. In turn, differences in rate and degree of ionization determine variations in absorption as well as local and toxic side-effects. The toxicity of mercurials is directly related to their rate of ionization: $RHgOH \rightleftarrows RHg^+ + OH^-$.

Diffusion across cell membranes plays an important role in the activity of mercury derivatives. Proteins apparently are first precipitated by mercuric ions, but redissolve these ions with complex formation. Mercurials thus dissolve more readily in serum than in water, and diffuse readily through living cells. The rate of diffusion is enhanced by ammonium chloride, potassium iodide (formation of a more diffusible potassium mercuritetraiodide) and other salts.

It has been shown that mercurials act by inactivating sulfhydryl groups of thiol-containing enzyme systems for 8–10 hours. Like that of organic arsenicals, the effect of mercury compounds can be inhibited by BAL (Chapter XXXII), and this compound as well as its congeners (BAL glucoside, thiosorbitol) have been used successfully to overcome mercury poisoning. Where the enzyme system affected by mercury is located, or acts, is unknown, but since the action of mercury seems to be limited to the kidney, it may be sought in this organ. The prompt termination of mercurial diuresis by BAL confirms this thought; on the other hand, monothiol

[13] Feinberg, Isaacs, and Boikan, *Am. J. Med. Sci.*, **218,** 298 (1949). Ruskin, Johnson, and Roddy, *Federation Proc.*, **8,** 329 (1949).

compounds which tie up mercuric ions less firmy than dithiols inactivate only the effects of these ions on the heart but do not affect diuresis.

IV. ANTIDIURETICS

Compounds which decrease the formation of urine from blood are called antidiuretics. Their main—and only useful—representative is the proteinogenous hormone of the posterior lobe of the pituitary gland (Pitressin) of unknown structure. Administered parenterally, or by diffusion through the nasal mucosa, it is used principally to cut down the volume of urine in *diabetes insipidus*.

The antidiuretic principle found in the edematic fluid of patients suffering from cirrhosis of the liver or of cardiac edema differs perhaps from Pitressin. It may be identical with ferratin, a protein-type hormone concerned with absorption and storage of ferrous ions in the body.

CHAPTER XVI

Anticoagulants

I. FUNCTIONS AND USES

Anticoagulants are substances which prolong the coagulation time of blood. The prompt formation of a blood clot is an essential safeguard against excessive hemorrhage, but if a clot is produced within a blood vessel, a serious threat arises to the normal flow of circulatory liquids on which all vital organs depend for their metabolites, for their constant state of hydration and for the removal of their waste products. The maintenance of normal blood clotting time in the intact animal depends on a sensitive balance between coagulants (see Chapter XXVIII-II-7) and natural anticoagulants of the system. The most important anticoagulant in mammals is heparin which is produced by the mast cells close to the capillaries in various tissues of the body.

Intravascular clotting is a complex process, the explanation of which has taxed the ingenuity of biochemists and physiologists. It is not yet completely understood but a short—even though schematized—description of the processes involved should facilitate an understanding of the role of anticoagulants. It is illustrated in Figure 1.

The primary site of an intravascular clot is usually at a point where the endothelium of a blood vessel has been injured. The so-called platelets or thrombocytes agglutinate by a slowing of the blood stream and form a small initial clump (thrombus) around which the true blood clot is constructed. The latter consists essentially of the blood protein, fibrin. Some of the thrombocytes disintegrate and release a protein-type material called thromboplastin which, in the presence of calcium ions, converts the zymogen prothrombin to the enzyme thrombin.

The first small amounts of thrombin are deactivated by a natural antienzyme, the factor antithrombin from plasma. As more platelets disintegrate and release more thromboplastin, enough thrombin survives to convert the soluble protein, fibrinogen, to insoluble fibrin. Simultaneously, thrombin catalyzes the conversion of plasma accelerator globin to serum accelerator globin, and the latter in turn speeds up the activation of thrombin. This cycle makes the liberation of thrombin from prothrombin an autocatalytic process, and the formation of fibrin thus gathers momen-

tum. The fibrin clot grows, halts and captures more thrombocytes as well as leukocytes and red blood corpuscles and soon may block the flow of blood through the vessel.

Natural and synthetic anticoagulants may interfere with the course of these reactions at many points and by a variety of biochemical mechanisms. Some information concerning their mode of action is available for heparin

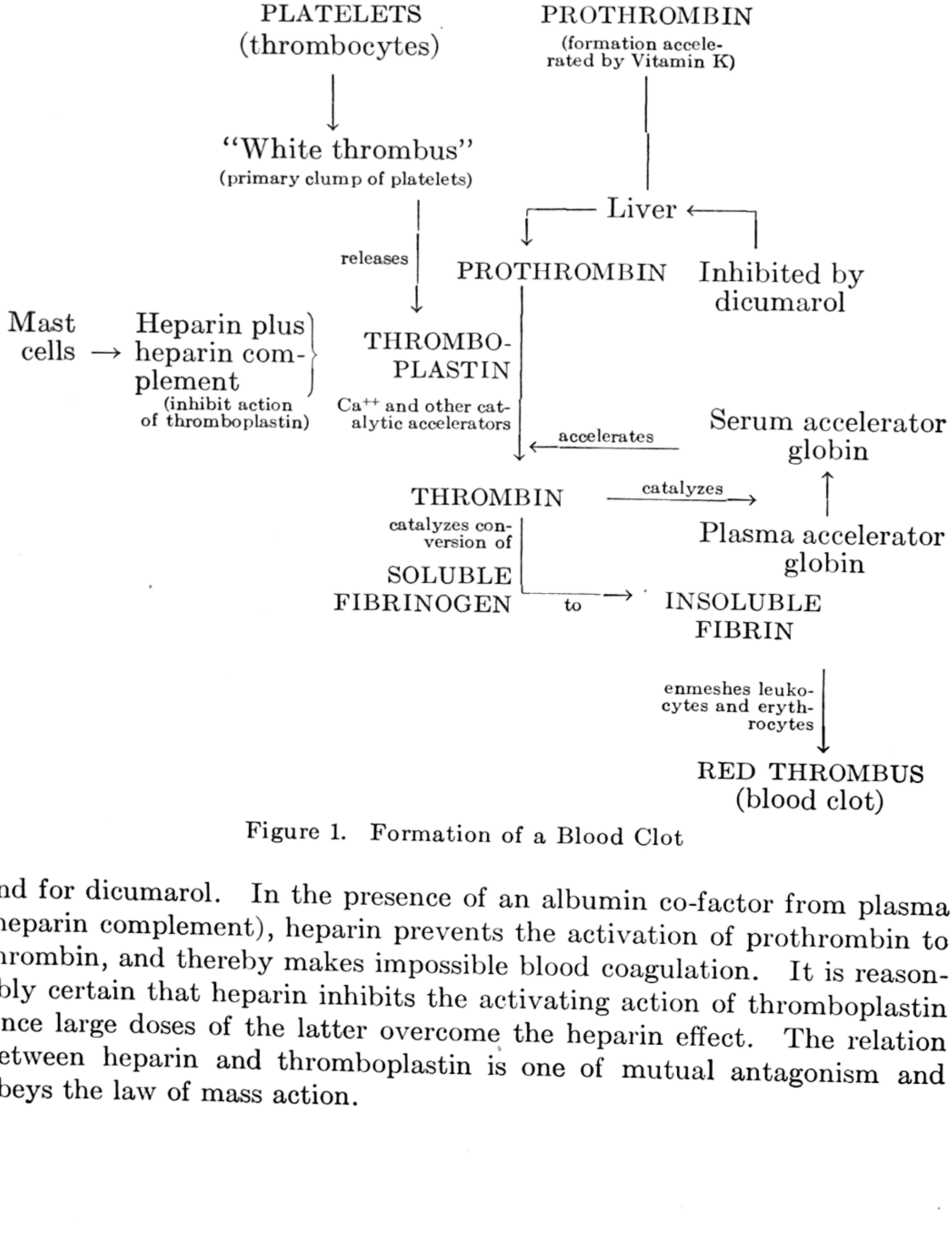


Figure 1. Formation of a Blood Clot

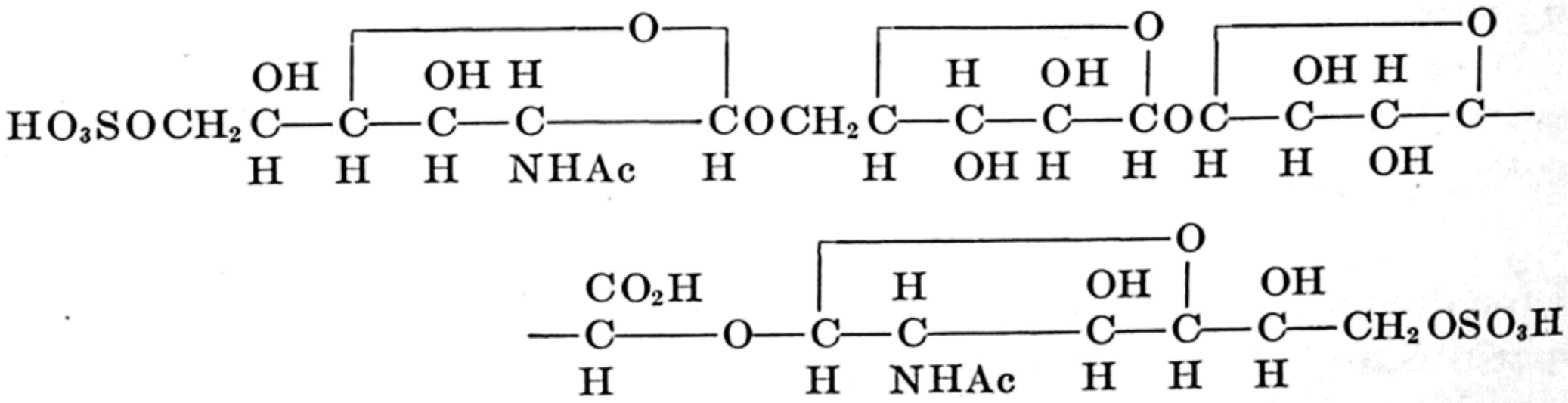
and for dicumarol. In the presence of an albumin co-factor from plasma (heparin complement), heparin prevents the activation of prothrombin to thrombin, and thereby makes impossible blood coagulation. It is reasonably certain that heparin inhibits the activating action of thromboplastin since large doses of the latter overcome the heparin effect. The relation between heparin and thromboplastin is one of mutual antagonism and obeys the law of mass action.

Dicumarol apparently attacks the clotting mechanism at a different point. It halts the synthesis of prothrombin in the liver, and this view of its mode of action is supported by the fact that dicumarol antagonizes the clot-promoting action of the coagulant naphthoquinones which are known to catalyze prothrombin formation in the same organ. Detailed discussions of these relationships and of additional factors involved in blood clotting have recently been presented.[1]

II. HEPARIN

Heparin was discovered by McLean[2] in the course of a purification of phosphatides from blood platelets. Its anticoagulant effects were studied by Howell[3] who recommended this non-toxic material for the treatment of disorders of coagulation. It was introduced into medicine in 1937.[4] As mentioned above, it is produced by the mast cells, and since the latter are found in great quantities in the lung and the kidney, these tissues are the common sources of the anticoagulant. Beef lungs are washed free from blood, dried and powdered, and extracted with 1% sodium chloride solution. Heparin is precipitated from the extract with acetone. Certain vegetable sources such as beans and peanuts also yield heparin on extraction.

Heparin is inactivated by methanol, a property generally exhibited by biologically active polysaccharides whose hydroxyl groups are esterified with sulfuric acid. It is also inactivated by aldehydes, and this appears to be a general property of active compounds containing amino groups. When heparin reacts with toluidine blue, it causes metachromasia, a change of the blue color of the dye to purple. This change is characteristic of high-molecular sulfate esters, for example chondroitin sulfuric acid (XVI-1) from cartilage, and muscoitin sulfuric acid.



(XVI-1)

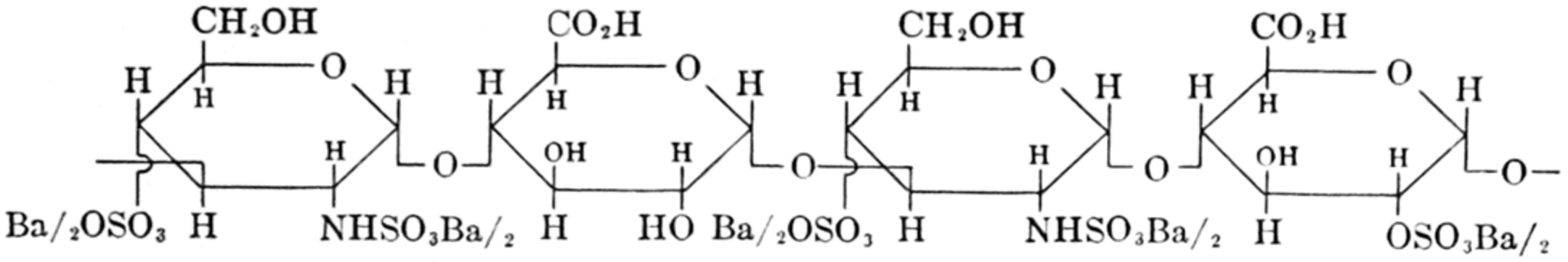
[1] Riggs, *New Eng. J. Med.*, **242,** 179 (1950). McIntosh, *J. Pharm. Pharmacol.*, **1,** 353 (1949).

[2] McLean, *Am. J. Physiol.*, **41,** 250 (1916).

[3] Howell, *Harvey Lectures*, **12,** 272 (1918).

[4] Murray, Jaques, Perret, and Best, *Surgery*, **2,** 163, (1937). Crafoord, *Acta. Chir. Scand.*, **79,** 407 (1937).

These substances contain only one sulfate ester group for each glucosamine-glucuronic acid pair, whereas three sulfuric acid groups are found in the same disaccharide section of heparin. For a homogeneous fraction of the crystalline barium salt, formula (XVI-2) has been proposed.[5]

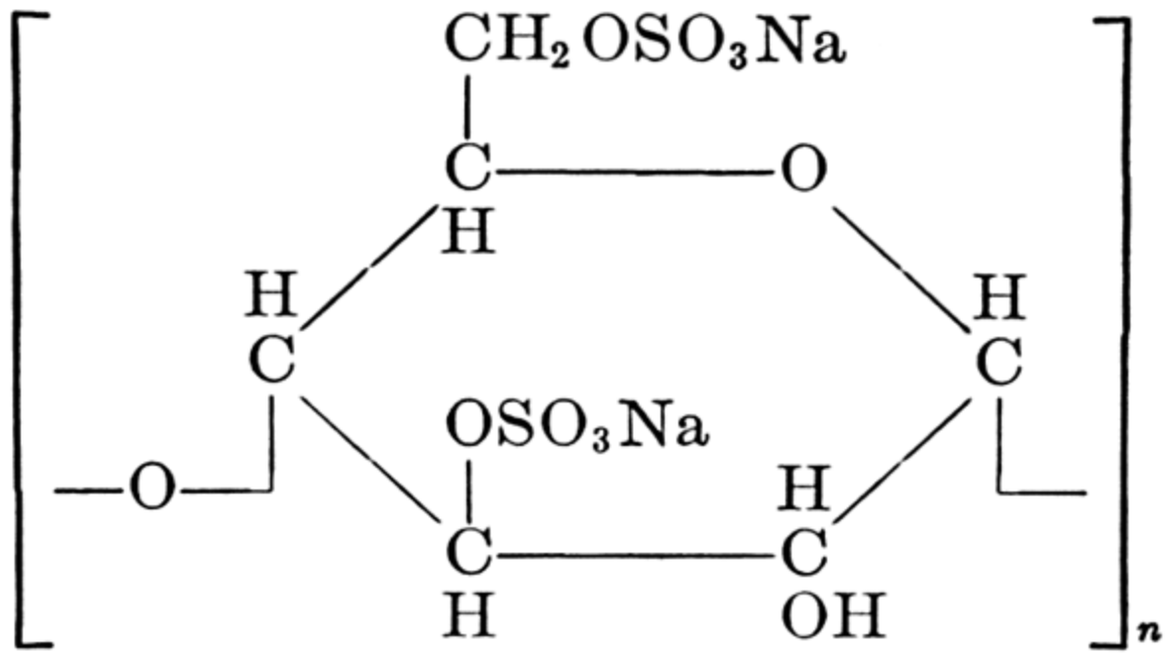


(XVI-2)

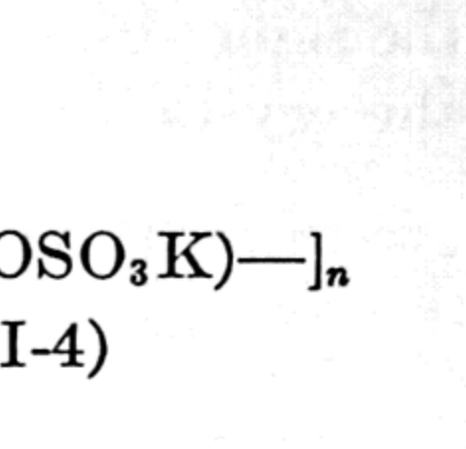
Heparin is a strong acid and combines with certain metallic ions (barium) and with proteins (salmin) to sparingly soluble salts. This fact complicates the isolation of heparin from tissue powder since the anticoagulant is inactivated if it combines with proteins. Since the action of heparin is only of relatively short duration, some of its sparingly soluble salts have been used for injections in order to prolong the anticoagulant effect. This procedure parallels the use of procaine-penicillin and similar insoluble salts which increase the duration of action of the antibiotic penicillin (Chapter XXXVIII).

Partial removal of the sulfate ester groups reduces anticoagulant activity; this trend can be observed also in different fractions of heparin having a decreasing content of sulfuric acid groups. The degree of esterification is, however, not the only criterion of activity since heparins from different species—presumably with different structural features—but of equal organic sulfate content exhibit wide variations of potency. When it was discovered that the trypanocidal drug Suramin (XXXVII-4) and the dyestuffs Pontamin Pink and Chlorazol Sky Blue had pronounced anticoagulant activity it was assumed that both aliphatic and aromatic polysulfonic or polysulfuric acids might share this property. Sodium cellulose disulfate (XVI-3) and potassium polyvinyl sulfate (XVI-4) have been tested successfully for prolongation of blood clotting time. Alginic acid disulfuric acid ester (XVI-5) has been reported to be a strong anticoagulant of low toxicity.

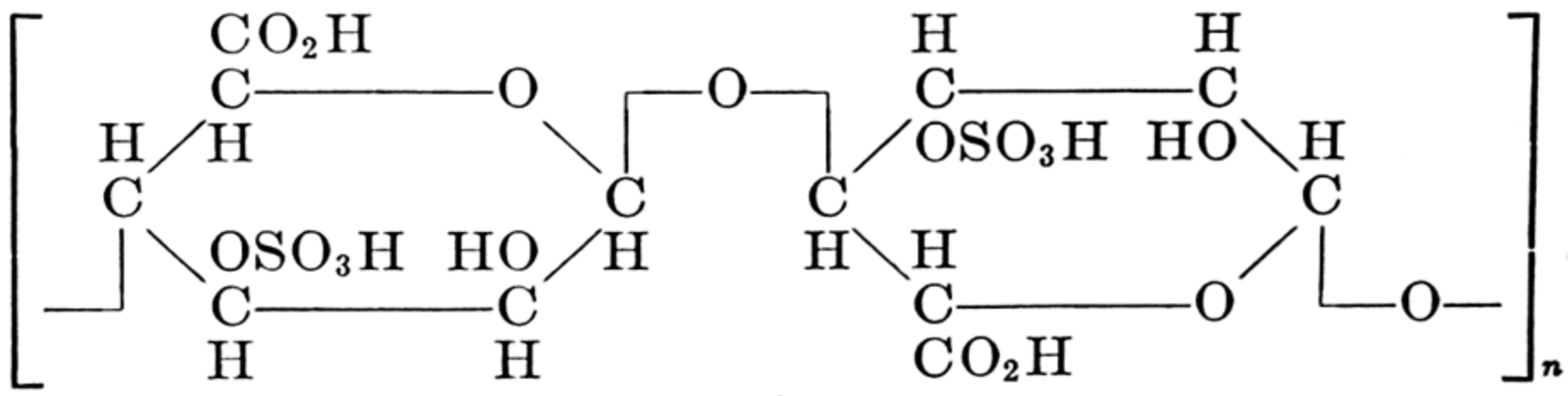
[5] Jorpes, *Heparin in the Treatment of Thrombosis. An Account of its Chemistry, Physiology and Application in Medicine*, 2nd Ed. Oxford Univ. Press, London, 1946. Jorpes, Boström, and Mutt, *J. Biol. Chem.*, **183**, 607 (1950). Wolfrom *et al.*, *J. Am. Chem. Soc.*, **72**, 5797 (1950).



(XVI-3)



[—CH$_2$CH(OSO$_3$K)—]$_n$
(XVI-4)



(XVI-5)

Heparin has been used in arteriosclerosis, in the treatment of thromboses, for the prevention of gangrene in experimental frostbite, and in other conditions in which blood vessels are obstructed or injured. The prolongation of the clotting time depends on the blood level of heparin, the logarithm of the clotting time being a linear function of heparin concentration.[6] Even after large doses heparin disappears from the blood after a few hours, perhaps by enzymatic destruction; this short duration of action of heparin has been the greatest stimulus in a search for other longer-lasting anticoagulants.

A group of anticoagulants which resemble heparin are found in the antithrombins (hirudins) which provide leeches, ticks and other blood-sucking animals with a clot-preventing mechanism. It has been postulated that a hirudin-like substance is also present in normal blood in small amounts.

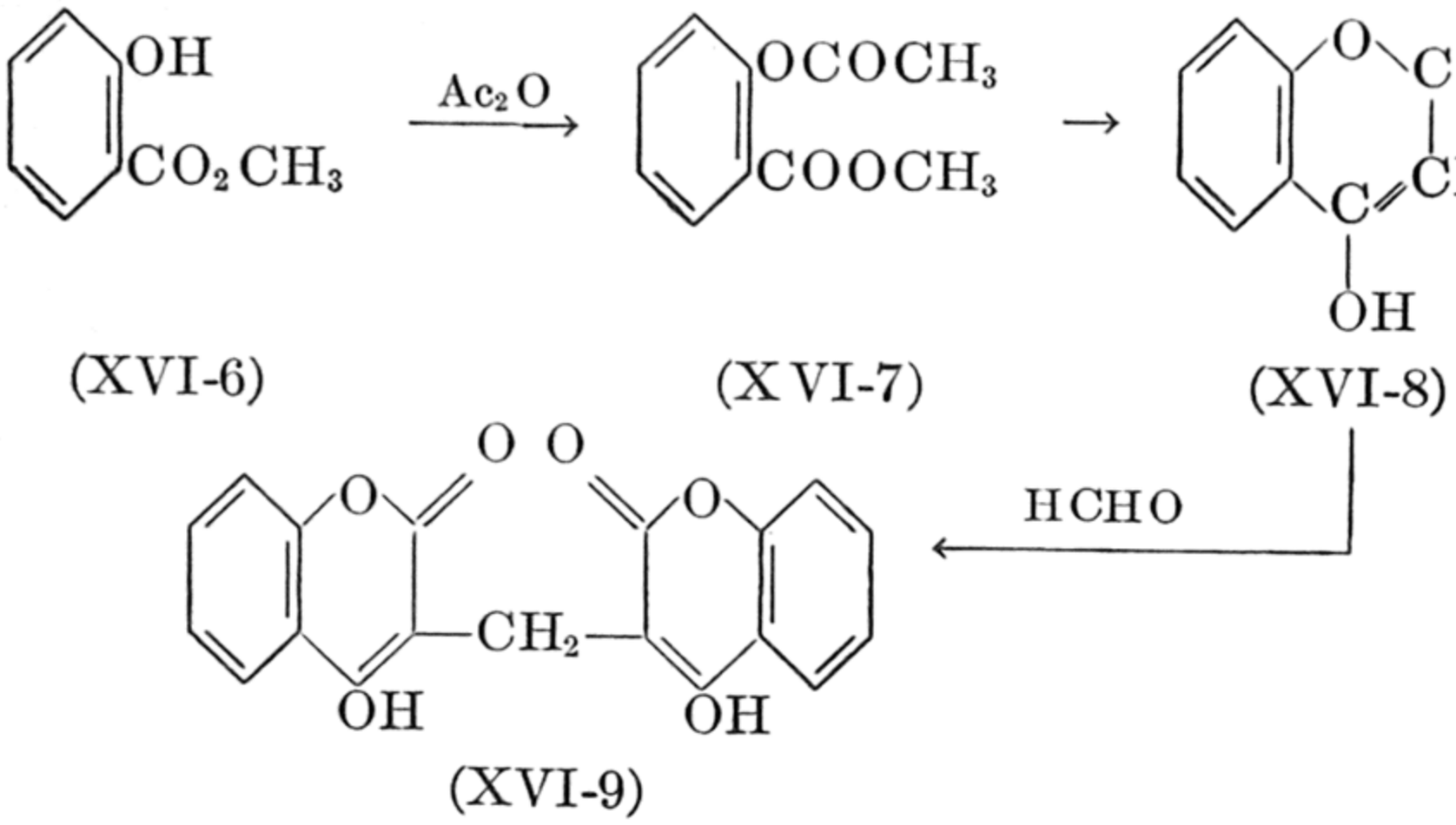
III. DICUMAROL

1. Origin, Synthesis and Function

Cattle feeding on spoiled sweet clover hay usually sicken and undergo serious, often fatal bleeding (sweet clover disease). This condition is caused by a sharp increase of the blood clotting time of the animals. The pathogenic hemorrhagic principle of sweet clover hay has been recognized as 3,3′-methylenebis-(4-hydroxycoumarin) (XVI-9) and has been

[6] Jaques and Ricker, *Blood*, **3**, 1197 (1948).

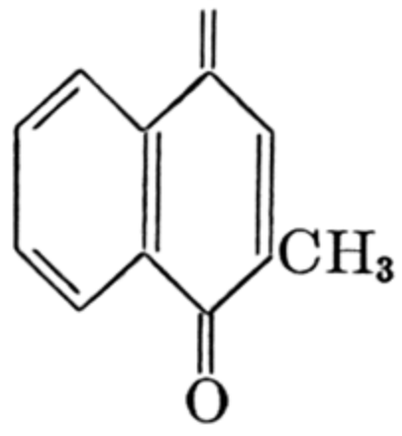
called dicumarin or dicumarol for short. The compound can be synthesized from methyl salicylate (XVI-6) through acetyl methyl salicylate (XVI-7), ring closure to 4-hydroxycoumarin (XVI-8), and combination of two moles of this reagent by means of formaldehyde.[7]



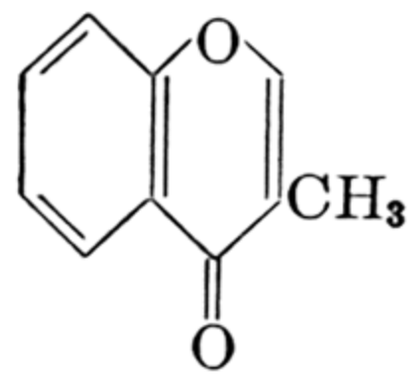
(XVI-6) (XVI-7) (XVI-8) (XVI-9)

Dicumarol is at present the leading drug against blood clotting in spite of two distinct disadvantages. Its onset of action is slow, and two to four days may pass before coagulation time is markedly raised. Its effect does then not wear off for four or more days after discontinuation of administration.

The mechanism of action of dicumarol has been elucidated to some extent. The drug inhibits serum cholinesterase *in vitro*[8] but most impressive is its antagonism to the blood clotting catalysts of the vitamin K group. It acts by interference with the utilization of naphthoquinone derivatives in the synthesis of prothrombin in the liver since some of the latter can prevent the effect of one small dose of the coumarin derivative. There exists a definite structural analogy between the keto form of 4-hydroxycoumarin and 1,4-naphthoquinone,[9] and consequently between the antihemorrhagic



(XVI-10)

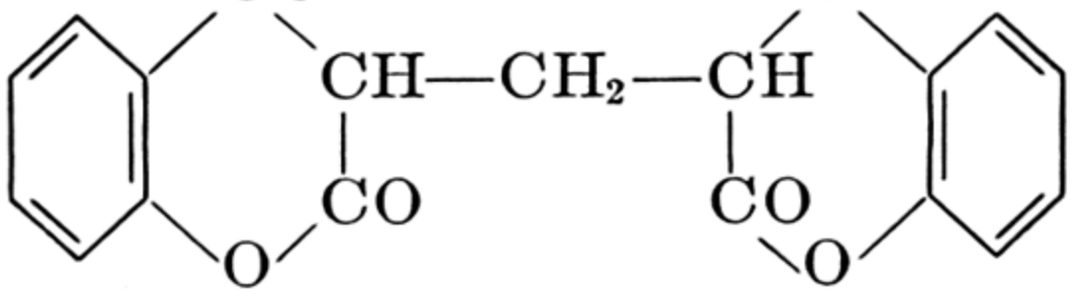


(XVI-11)

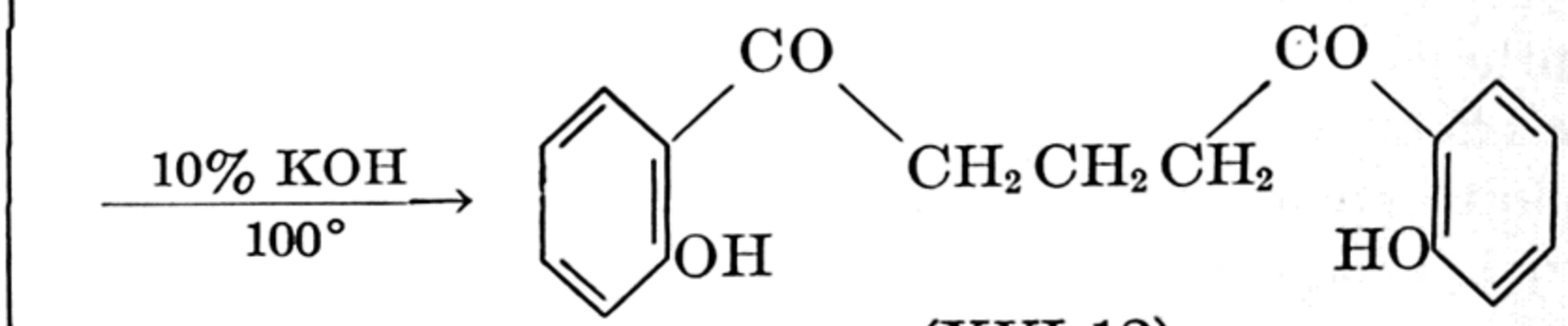
[7] Link, *Harvey Lectures*, **39,** 162 (1943–1944).
[8] Grossmann, Hais, and Kasalicky, *Nature*, **165,** 276 (1950).
[9] Quick, *Physiol. Revs.*, **24,** 297 (1944).

2-methyl-1,4-naphthoquinone (Menadione, XVI-10) and either half of the keto form of dicumarol. This similarity could be extended to include 3-methylchromone (XVI-11) but this compound has been found to have a weak activity like Menadione. On the other hand, the latter prevents completely the hemorrhagic effects of dicumarol in laboratory animals.[10]

Whenever a compound does not exert its specific known activity *in vitro*, one will have to suspect that it is altered to the truly active drug in the animal body. Dicumarol fits this description; the time lag before it becomes active *in vivo* is obviously the period during which it is converted to an active substance. The view has been expressed that the nature of this material might be understood from degradation reactions of dicumarol in the laboratory which had also played a major role in the elucidation of the chemical structure of the anticoagulant. When dicumarol is fused with potassium hydroxide at 300°, it is converted almost quantitatively to salicylic acid. This reaction proceeds through an intermediate δ-diketone, 1,3-disalicylylpropane (XVI-12) which can be isolated in near-quantitative yield from the alkaline hydrolysis of dicumarol, and yields, in turn, salicylic acid on alkali fusion.



(XVI-9, Keto Form)



The ease of formation of the δ-diketone (XVI-12) seemed to suggest that the latter has been formed by decarboxylation of the β-keto acid structure (hydrolyzed keto form) of dicumarol. Such a decarboxylation and subsequent fission of a δ-diketone could well take place *in vivo* under

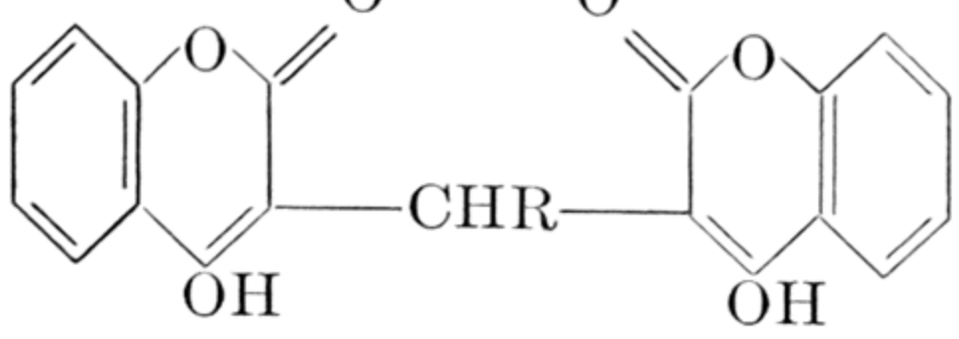
[10] Meunier and Mentzer, *Bull. soc. chim. biol.*, **25,** 80 (1943).

the influence of enzymes.[11] It was logical, therefore, to study the anticoagulant effect of salicylic acid.

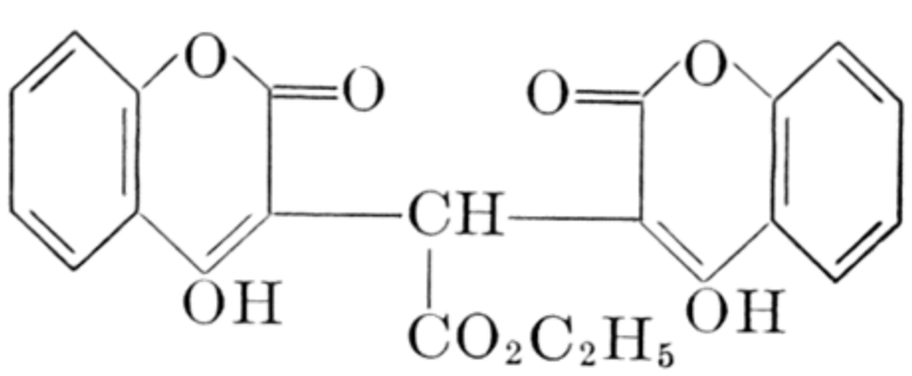
Salicylic acid and its esters produce an increase in prothrombin time, and this delay in blood coagulation can be prevented by the natural or the synthetic K-vitamins. This effect is of a much lower order than that of dicumarol and the degradation of dicumarol to salicylic acid is probably not the mechanism by which the compound acts. The competition with naphthoquinones due to spatially similar relations is more widely accepted as an explanation of its activity.

2. Structural Variations

In view of the possibility that dicumarol may arise in sweet clover by condensation of two molecules of 4-hydroxycoumarin with formaldehyde as in its laboratory synthesis, an extended series of compounds of type (XVI-13) which can be formed from 4-hydroxycoumarin and higher or substituted aldehydes has been investigated for anticoagulant action. While none of these compounds had been reported originally to approach dicumarol in activity,[12] ethyl bis (4-hydroxy-3-coumarinyl) acetate (XVI-14)[13] has recently been introduced under the name of Tromexan.



(XVI-13)



(XVI-14)

Its onset of action is no more than 24 hours, and it does not prolong coagulation time more than one day after termination of the treatment. It is said to have few toxic effects and may be four times more active than dicumarol.

Isosteres of dicumarol in which the cyclic oxygen atoms are replaced by sulfur or imino groups have been tested but do not approach their natural prototype in anticoagulant activity. 3,3′-Methylenebis-(4-hydroxy-1-thiocoumarin) (XVI-15) exhibits one tenth, and 3,3′-methylenebis-(4-hydroxy-2-quinolone) (XVI-16) only one fiftieth the activity of dicumarol.[14] On

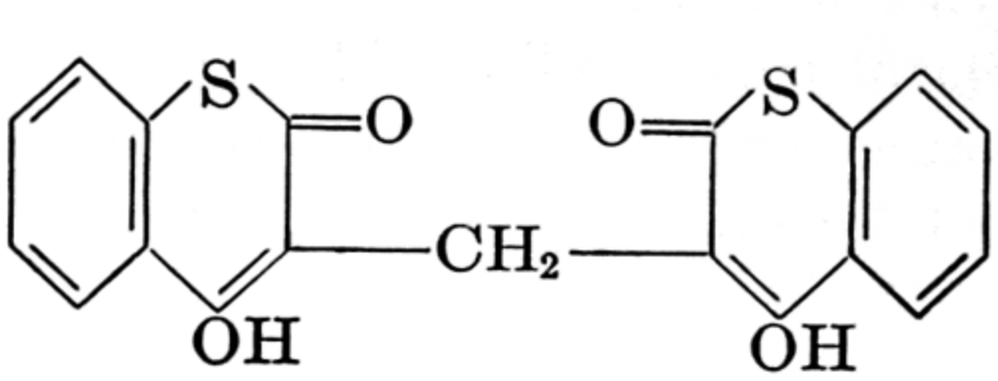
[11] Stahmann, Huebner, and Link, *J. Biol. Chem.*, **138,** 513 (1941).

[12] Overman, Stahmann, Huebner, Sullivan, Spero, Ikawa, Graf, Roseman, and Link, *J. Biol. Chem.*, **153,** 5 (1944).

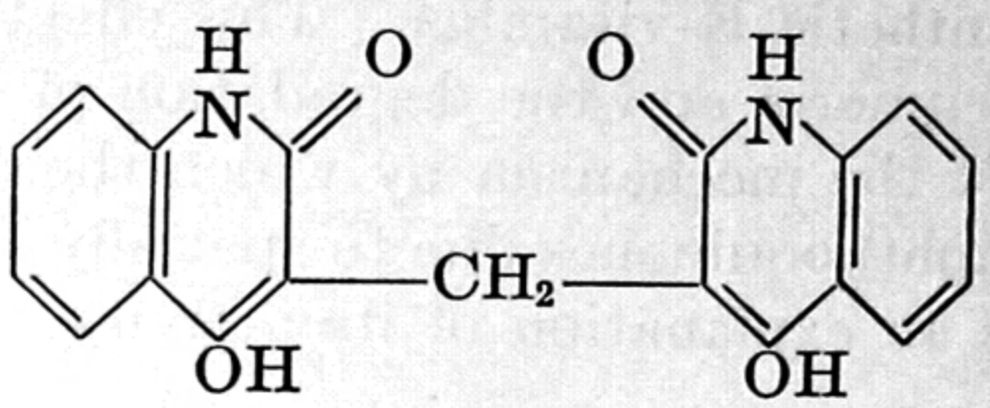
[13] Deutsch, *Schweiz. med. Wochschr.*, **78,** 785, 806 (1948); **79,** 1010 (1949). Burt, Wright, and Kubik, *Brit. Med. J.*, **2,** 1250 (1949).

[14] Mentzer, Meunier, Buu Hoï, and Cagniant, *Bull. soc. chim. biol.*, **25,** 384 (1943).

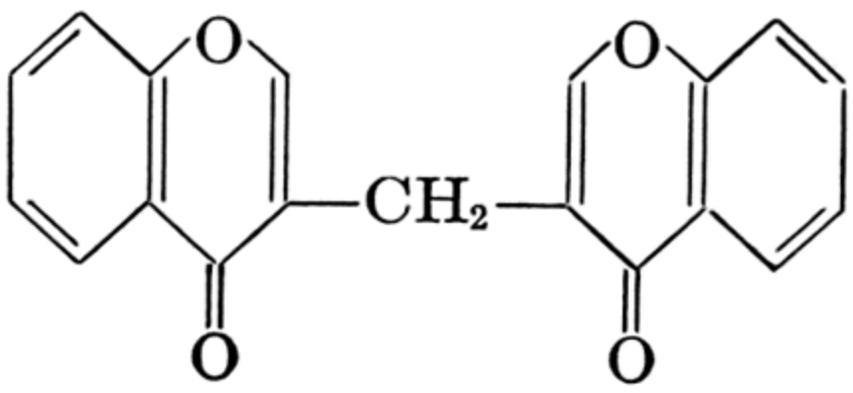
the other hand, 3,3′-methylenebischrome (XVI-17) possesses weak vitamin K activity, and this property is shared by 3,3′-methylenebis-(2-hydroxy-1,4-naphthoquinone) (XVI-18) which incorporates some of the features of dicumarol, and of phthiocol (Chapter XXXVI).



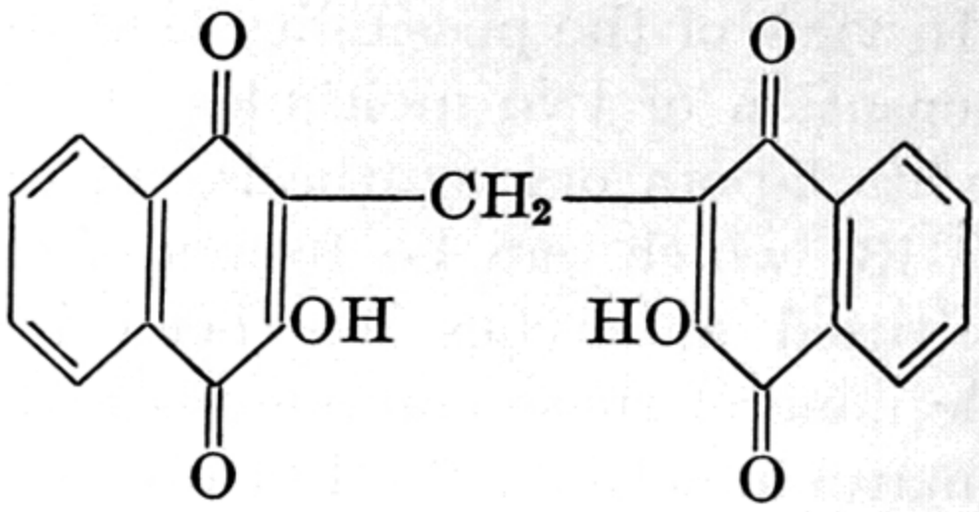
(XVI-15)



(XVI-16)

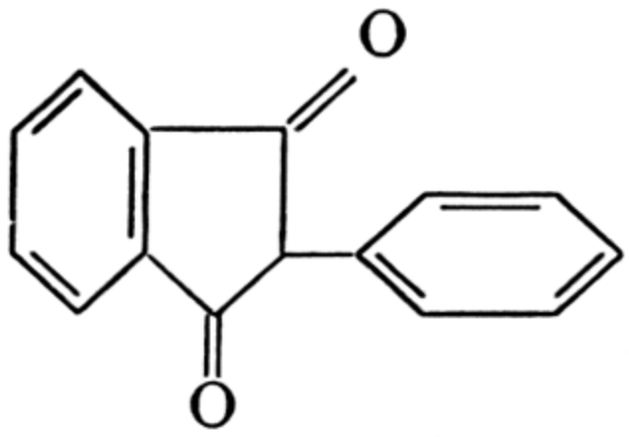


(XVI-17)



(XVI-18)

An investigation of 2-phenyl-1,3-indanedione (XVI-19) was prompted by the structural similarity of this compound to anticoagulant coumarin derivatives. 2-Phenylindanedione (PID) appears to exert a more rapid and constant effect than dicumarol, and has been given clinical trials.[15]



(XVI-19)

[15] Soulier and Gueguen, *Rev. d'Hématol.*, **3,** 180, 184, 195 (1948).

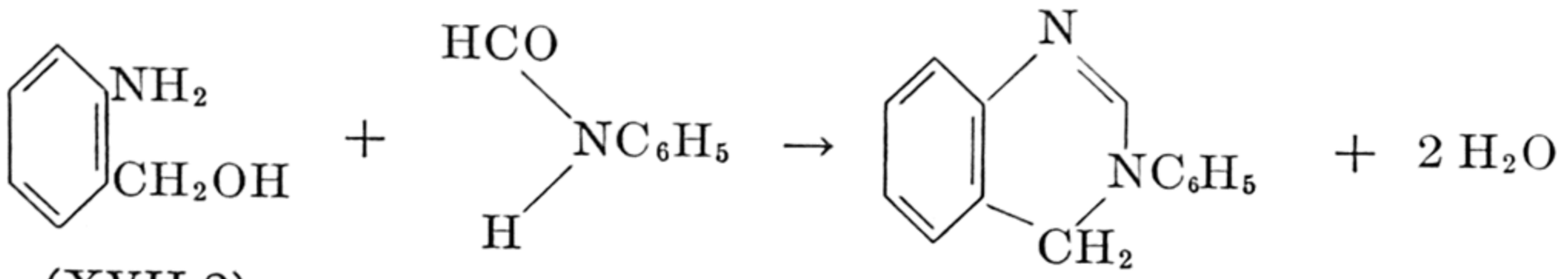
CHAPTER XVII

Drugs Eliciting Symptoms in the Gastro-intestinal Tract

I. APPETITE STIMULANTS

Several drugs which cause the stomach to contract and thereby to simulate hunger can be used as aperitives or appetite stimulants. The hunger contractions are of central origin, and may be accompanied by stimulation of salivary excretion and other effects which combine to give the picture of appetite. The alkaloid strychnine, a central stimulant, is used in tonics for this purpose. Almost all the popular appetite tonics contain bitter principles, particularly quinine. Iron salts are added occasionally for their hematopoietic effect.

One of the most satisfactory appetite stimulants is 3-phenyl-3,4-dihydroquinazoline (XVII-1) which has been marketed under the name of Orexin. Its hydrochloride tastes so bitter that the insoluble tannate is commonly used. This salt is converted to the soluble hydrochloride by the gastric juice.[1] The drug is best prepared by the action of formanilide on *o*-aminobenzyl alcohol (XVII-2).



(XVII-2) (XVII-1)

II. ANTIAPPETITE DRUGS (ANOREXICS)

Overeating is the main cause of obesity, and obesity contributes much to diseases of the heart and blood vessels, particularly in aged individuals. Any drug which counteracts hunger contractions and thereby breaks the habit of overeating renders a valuable service to the obese patient.

The anorexic drug used most widely in the United States is Dexedrine, (+)1-phenyl-2-aminopropane, $C_6H_5CH_2CH(CH_3)NH_2$. The chemistry of

[1] May and Dyson, *Synthetic Drugs*, 4th ed. Longmans, Green, New York, 1939, p. 326.

this compound will be discussed in Chapter XIX. The (—) isomer exhibits only negligible anorexic action. The drug also suppresses the sense of taste for sucrose,[1a] and it seems possible that anorexia is related to depression of olfaction.

The *para*-methyl derivative of Benzedrine possesses analgetic and anorexic effects with barely any stimulation of the central nervous system[1b].

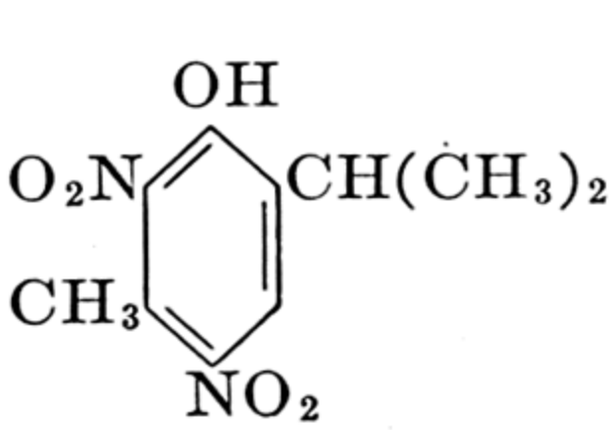
III. TOXIC DRUGS AS WEIGHT REDUCING AGENTS

Several dinitrophenols have been used ill-advisedly as therapeutic weight reducing agents, but have been abandoned because of their numerous dangerous toxic manifestations. They are treated here because their use has not yet been completely eradicated.

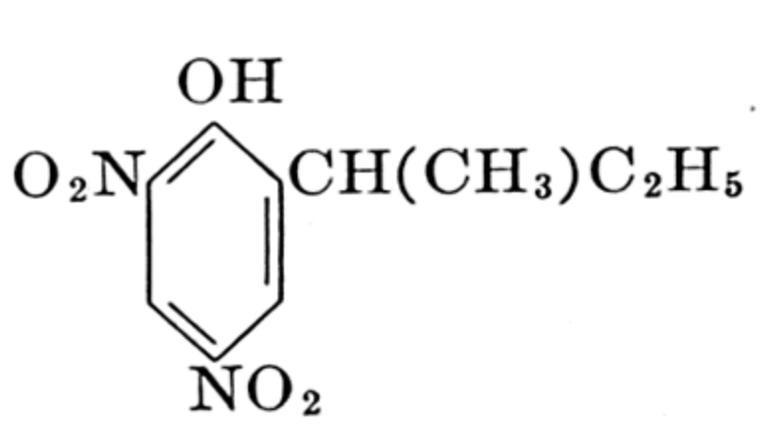
The most extensive investigations have centered around 2,4-dinitrophenol. This compound is a powerful oxidizing agent and raises the rate of basal metabolic reactions in a way comparable to the effect of thyroxine (Chapter XXVI). The biochemistry and toxicology of 2,4-dinitrophenol have been reviewed in a recent monograph.[2]

Dinitro-*o*-cresol (3,5-dinitro-2-hydroxytoluene) also stimulates the metabolism, raises the body temperature and causes toxicity symptoms like dinitrophenol, but in a more marked degree. Because it catalyzes the oxidative destruction of non-carbohydrate material, it has been used as a weight reducing agent.

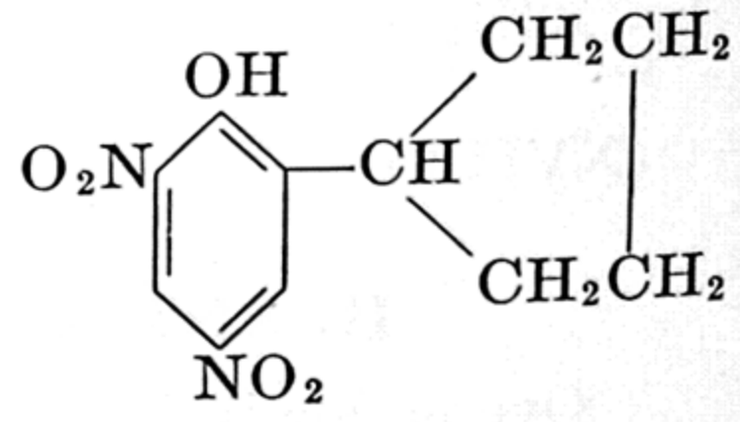
A number of other dinitrophenols have been prepared and tested in the hope of finding some compound with a similar effect on the metabolism, but less toxic. 2,4-Dinitrothymol (XVII-3) is more active than dinitrophenol, and apparently less toxic than dinitrocresol.[3] Rats kept on a diet of 2-*sec*.-butyl-4,6-dinitrophenol (XVII-4) gained less weight than control animals and showed otherwise no ill effects.[4] 2,4-Dinitro-6-cyclo-



(XVII-3)



(XVII-4)



XVII-5)

[1a] Ahokas, Payne and Goetzl, *Permanente Found. M. Bull.*, **8,** 112 (1950).
[1b] Macko, Fellows and Fendrick, *Feder. Proc.*, **9,** 299 (1950).
[2] von Oettingen, *Phenol and Its Derivatives. The Relation between Their Chemical Constitution and Their Effect on the Organism.* National Institutes of Health Bulletin No. 190, U. S. Government Printing Office, Washington, D. C., 1949, pp. 237–275.
[3] Heymans and Casier, *Arch. intern. pharmacodynamie,* **50,** 20 (1935).
[4] Spencer, Rowe, Adams, and Irish, *J. Ind. Hyg. Toxicol.*, **30,** 10 (1948).

pentylphenol (XVII-5) is more active than dinitrophenol in stimulating the metabolism of laboratory animals, and is probably not as toxic as that substance.[3] The corresponding cyclohexyl homolog behaves similarly.

IV. GASTRIC ANTACIDS AND DIGESTANTS

Excessive secretion of gastric hydrochloric acid leads to unneeded peptic activity and endangers the mucous lining of the stomach. Prolonged action of excess hydrochloric acid can lead to ulceration of the gastric and duodenal mucosas. On the other hand, reduction of the normal percentage of gastric hydrochloric acid by alkalizing agents is just as disadvantageous as leaving unchecked a pathologically high concentration of stomach acid, and buffers and alkalizers must be used with care in hyperacidity.

Sodium bicarbonate, magnesium oxide, magnesium hydroxide (milk of magnesia), bismuth salts, basic phosphates, calcium carbonate or citrate are the common neutralizing agents for excess stomach acid. If the stomach wall is irritated by ulceration and produces more acid which in turn worsens the lesions, the ulcers can be coated and allowed to heal under protective colloidal films. For this purpose, gelatinous materials have been found suitable. Aluminum hydroxide gel and magnesium trisilicate are colloids which combine with this state the ability to neutralize hydrochloric acid. Other aluminum salts used are basic aluminum aminoacetate, $Al(OH)_2OCOCH_2NH_2$, and the aluminum salts of bile acids. Ulcers can also be covered by the colloidal polysaccharide mucin which is manufactured from the membranes of hog stomachs. Enterogastrone, one of several substances secreted by the mucous lining of the upper intestinal tract of hogs, has also been used to treat peptic ulcers with good success.

While studying the pharmacological behavior of the antimalarial drug, Paludrine (Chapter XXXV) it was discovered that this compound exerts a powerful inhibitory action on the secretion of gastric hydrochloric acid. This application of Paludrine is still in the state of development.

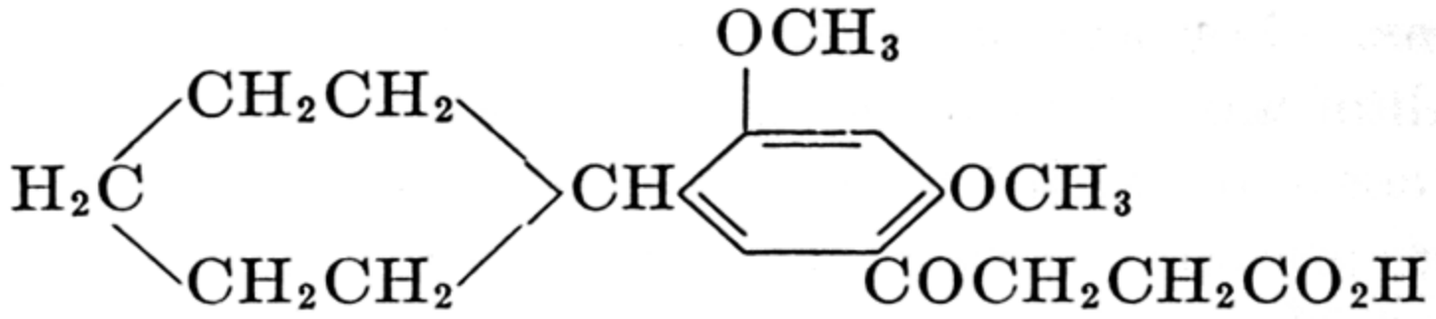
It should be pointed out that this is one of the few cases in which the secretion of gastric acid is causatively decreased. The common antacids are only neutralizing agents. Secretion of gastric hydrochloric acid is catalyzed hormonally by histamine and controlled by impulses transmitted by the vagus nerve. Only correction of vagus hyperactivity can relieve the cause of hyperacidity.

Cases of hypochlorhydria (lack of gastric hydrochloric acid) are attributable to pernicious anemia, gastric cancer and other serious disorders, but occasionally certain otherwise healthy individuals exhibit this de-

ficiency. Their lack of stomach acid can be overcome by regular ingestion of 0.2% hydrochloric acid, either as such, or of hydrogen chloride adsorbed on charcoal or other carriers which tend to mask its sour taste.

Achlorhydria is occasionally accompanied by a lack of pepsin, the proteolytic enzyme of the stomach. This is not surprising if one considers that pepsin operates best at pH 4.5 maintained by normal concentrations of stomach acid. Pepsin prepared from hog stomach is administered in such cases together with hydrochloric acid.

Certain disorders of the liver call for ingestion of bile salts (choleretics) which are ordinarily provided for by this organ. The most important bile salts are obtainable from ox bile for therapeutic purposes and consist of sodium taurocholate and sodium glycocholate. They are double salts of sodium taurate ($H_2NCH_2CH_2SO_3Na$), and sodium glycinate (H_2NCH_2COONa), respectively, with the sodium salts of bile acids, particularly sodium cholate. The chemistry of these compounds may be found in standard texts of organic chemistry. The pharmacodynamic value of bile salt therapy is questionable. Recently, 4-keto-4-(2,4-dimethoxy-5-cyclohexyl)butyric acid (XVII-5a) has been shown to possess powerful and long-lasting choleretic properties.[4a]



(XVII-5a)

V. ANTABUSE (ABSTINYL)

Tetraethylthiuram disulfide, also called Antabuse or Abstinyl, is a drug which causes acute intolerance for ethyl alcohol by disturbing the oxidation of alcohol in the body and stopping alcohol metabolism at the stage of acetaldehyde.[5] The latter causes angioneurotic edema expressed by such symptoms as pulse acceleration, edema under the eyes, nausea and vomiting. Acetaldehyde is excreted through the lungs and the breath acquires the characteristic odor of this substance. Antabuse (XVII-6) has been used successfully in the treatment of alcoholism.



(XVII-6)

[4a] Burtner, Abstracts, 118th Meeting, Am. Chem. Soc., Chicago, Sept. 6, 1950.
[5] Jacobsen and Martensen-Larsen, *Nord. Med.*, **40,** VII (1948); *J. Am. Med. Assoc.*, **139,** 918 (1949).

VI. CONSTIPATING AGENTS

Constipating agents are used to counteract the symptoms of diarrheas. Excluded from this definition are drugs which combat the causative pathogenic organisms of infections of the alimentary canal which result in diarrhea.

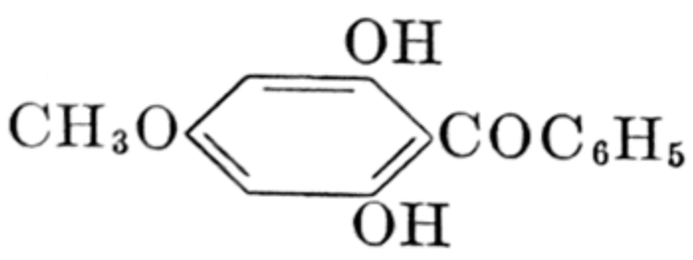
1. Bulky Constipants

Three general ways involving drugs to stop diarrhea are used by the medical practitioner. One of them depends on filling the colon with a hydrophilic bulky material which absorbs watery stools and promotes greater viscosity of intestinal contents. Pectin from apples and other fruits is the most favorite product for this purpose. Magnesium silicate, kaolin and other insoluble aluminum salts, charcoal, as well as materials which swell or are readily hydrated to voluminous masses, are also widely used.[6]

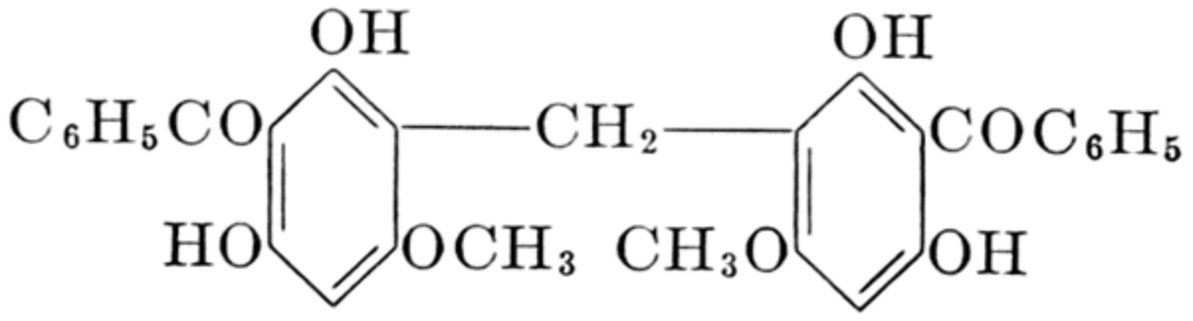
2. Opium and Cotoin

The second route works by a local nervous mechanism utilizing the varied manifestations of morphine (Chapter XI). The constipating action of opium (Paragoric), or the combined alkaloidal salts of opium (Pantopon) is caused almost entirely by the morphine content of these mixtures. The weakly antispasmodic properties of another opium alkaloid, papaverine, counteract the increase of the tone of the musculature of the bowel which becomes prominent after the disappearance of the peristaltic waves under the influence of morphine.

Cotoin (2,6-dihydroxy-4-methoxybenzophenone, XVII-7) is the active principle of the Coto bark.[7] It abolishes diarrhea by a similar mechanism as morphine. It has not been used much because of its extremely



(XVII-7)



(XVII-8)

bitter and sharp taste but derivatives prepared by the action of formaldehyde on cotoin have been introduced as tasteless improvements on their prototype. Methylenedicotoin (XVII-8) is a representative of this class of compounds. It is supposed to be a more powerful antidiarrhetic drug than cotoin.

[6] Emery, *J. Am. Med. Assoc.*, **108,** 202 (1937).
[7] Fränkel, *Die Arzneimittelsynthese*, 6th ed. Springer, Berlin, 1927, p. 770.

The constipating action of other classes of compounds has been observed occasionally during pharmacological tests for different types of activity. *m*-Phenylenediamine appears to check diarrhea, but the mechanism of its action has not become known.

Many neurological and psychosomatic disorders find their expression in spasticity of the intestines, that is, high sluggishness of the intestinal muscles, because disturbances of enzymatic acetylcholine destruction underscore the effects of this hormone (Chapter XXI). Antispasmodic drugs, especially atropine, can alleviate these conditions. They will be discussed in Chapter XXIII.

3. Astringents

Compounds which give more or less firmly bound colloidal precipitates with the albuminoid portions of epithelial cells, and with cell secretions can counteract diarrhea by their astringent action. The most important therapeutic agents of this type are the tannins, calcium hydroxide and certain metallic salts. In addition to their antidiarrhetic action, they are used as etching and membrane-contracting drugs on inflamed and chafed surfaces and mucose membranes, and in the protein-coagulant treatment of burns.

The tannins are water-soluble glucosides of polydepsides, polymeric esters of gallic acid. They are found in nature in various forms. Tannic acid (tannin) is usually prepared from nutgalls, which exude from oak twigs to encapsule the eggs of insects laid under their bark. They are pale-colored powders which can be hydrolyzed by dilute acids to gallic acid (3,4,5-trihydroxybenzoic acid) and glucose. The chemistry of tannin has been studied by Emil Fischer, and further details of its structure have been investigated by Russel.

Tannin is weakly acidic and acts both by virtue of its colloidal particle size and its structural characteristics. It is hydrolyzed enzymatically, and some efforts have therefore been made to preserve tannin if it is to exert its activity in the duodenum. The alcoholic acetyl esters of tannin are almost tasteless powders, insoluble in neutral or acid medium, but soluble in dilute alkali; they precipitate proteins in the intestine and combat diarrhea successfully.

Dilute calcium hydroxide solutions act as astringent constipating agents by precipitating fatty acids as calcium salts and neutralizing excess mineral acids. Their detergent activity aids in removing mucus from inflamed membranes and thus facilitates cleansing processes. A decrease of the excitability of the autonomic innervation of the intestines by calcium ions has also been noted.

Other metallic compounds which have been used against diarrhea include basic bismuth nitrate, $Bi(OH)_2NO_2$, which coats non-denuded

mucus membranes with a film protecting them from the effect of excess secretions.

VII. CATHARTICS AND EMETICS

1. Cathartics

The desire to purge the system of noxious products and to relieve constipation by means of drugs is one of the oldest ideas of medicine and self-medication. Chemicals from the plant and mineral world have been used by ancient and modern man as cathartics (*καθάρτικος* = purifying), purgatives or laxatives (laxao = to loosen). They constitute the most widely used—and abused—drugs, combining considerable scientific interest with economic value. Both pure natural and synthetic compounds, as well as pharmaceutical herbal mixtures are represented in large numbers in this series, because the rapid and readily observable action of laxatives in accelerating and increasing the evacuation of the bowels has made possible many observations of cathartic activity among widely different chemicals.

Several classifications of laxatives have been proposed, based on the type of evacuation they produce, or based on their physiological mode of action. Although the physical consistency of the stools, and the speed with which they are evacuated, are of considerable interest to the practitioner, the medicinal chemist will prefer to combine this classification of laxatives with the more scientific aspect of their mechanism of action. Within each group, further classification according to the chemical structure of the drugs can be arranged conveniently.

Irritants increase the motor activity of the intestinal walls, and thus propel the intestinal contents rapidly toward the site of expulsion. Mild irritation results in improved peristalsis accompanied by soft evacuation, because fluids ordinarily absorbed from the intestine have no time to pass through the intestinal wall. Among the irritants in this category are phenolphthalein, Isacen and certain anthraquinone derivatives.

Other irritants have a more drastic effect and act as hydragogs, producing watery stools. They cause retention of large amounts of water in the intestine by creating high osmotic pressures and withdrawing fluid from the circulation in order to dilute their own solutions. They are particularly effective if they are not readily absorbed themselves; the saline cathartics, sodium and magnesium sulfate, magnesium hydroxide (milk of magnesia), magnesium citrate and carbonate belong in this group.

Certain glyceride-type oils, and the so-called resinous cathartics exert their action by irritation of the small intestine. It will be shown that their mechanism of action may involve a denuding of the intestinal epithelium by removal of lecithins. The mode of action of calomel

(Hg_2Cl_2), a widely used purgative, is not quite clear; this reagent seems to interfere with the normal conversion of the bile pigment biliverdin to bilirubin in the large intestine.[8]

Bulk cathartics are indigestible materials which add volume to the feces and absorb water. Bran, agar, psyllium and Plantago seeds and other hydrophilic fibers and gums, including hemicellulose, and esters and ethers of cellulose, such as sodium carbomethoxycellulose, produce semi-solid stools.

Perhaps the most harmless way of counteracting the slow movement of the feces in constipation is to lubricate the intestines with paraffin oil (liquid petrolatum, mineral oil). This material also improves the peristaltic waves in the stomach and the intestines. The only disadvantage of this medication lies in the solubility of carotinoid and steroid vitamins in aliphatic hydrocarbons, and vitamins A and D may thus be lost to the system.

Elimination of feces in constipation can also be induced by the time-honored device of enemas. Cold water introduced into the colon, warm soap solutions, soap or glycerol suppositories, as well as salt solutions or ointment-like paraffin-olive oil mixtures have been used successfully in this procedure.

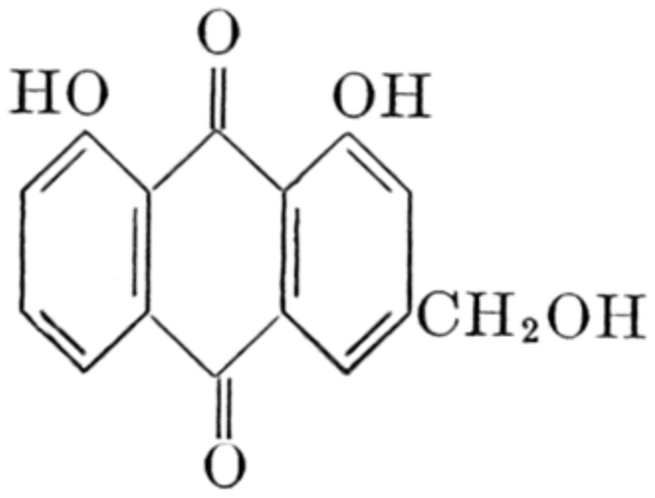
a. Anthraquinone Cathartics

A number of dried leaves, roots and liquid extracts of a variety of Frangula, Rumex, Polygonum, Rheum and Aloe plants contain anthraquinone derivatives which exert mild laxative activity. The active principles occur as glycosides and can be obtained by hydrolysis of these compounds. The most prevalent anthraquinone in all the plant species is emodin (1,6,8-trihydroxy-3-methyl-9,10-anthraquinone). It is doubtful that the anthraquinone content of the plants *per se* is solely responsible for the cathartic action of the latter. Emodin itself does not possess laxative properties worth mentioning, and it may be that a metabolic product constitutes the active principle. Chrysophanic acid, another anthraquinone derivative of this series, is also inactive but yields, on oxidation, a mixture of substances which are energetic purgatives. A similar change could occur in the organism.

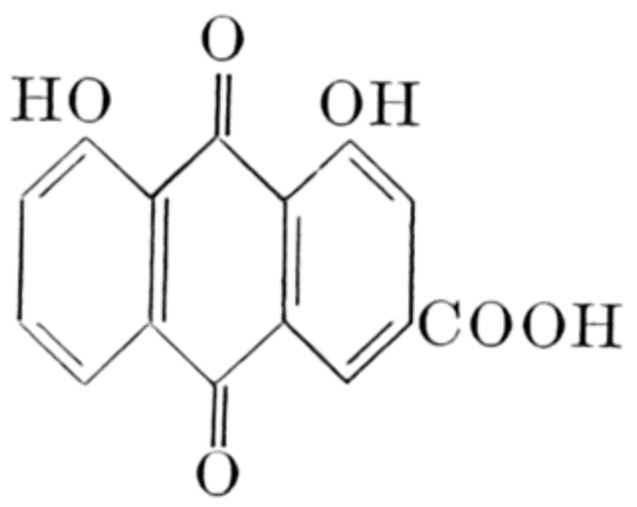
The pharmaceutical profession usually calls all the drugs in this series the emodin group. The cathartic action of these materials had been recognized by ancient peoples, Arabians, Chinese, African and West Indian natives and California Indians. Even today, the active principles are still not isolated but the plant materials are administered in suitable tablets, powders, and tinctures.

[8] Schmidt, Beazill, Atkinson, and Ivy, *Am. J. Digest. Diseases*, **5**, 613 (1938).

The most widely used laxative of our day is the drug Senna, obtained from the fruity pods or leaves of the Mediterranean plant *Cassia senna*.[9] It contains aloe-emodin (3-hydroxymethylchrysazin or 1,8-dihydroxy-3-hydroxymethylanthraquinone, XVII-9) and rhein (1,8-dihydroxyanthraquinone-3-carboxylic acid, XVII-10) as its chief active components. The latter is undoubtedly an oxidation product of aloe-emodin.

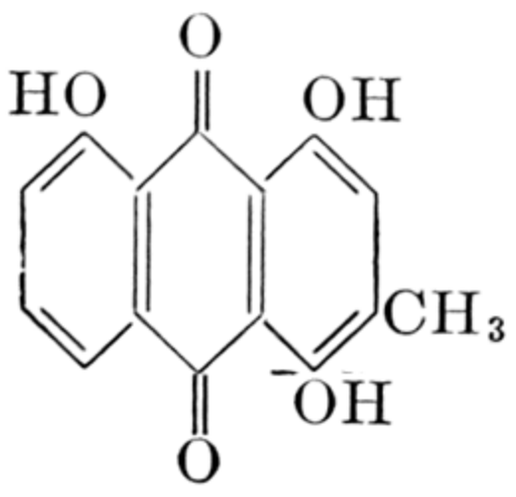


(XVII-9)

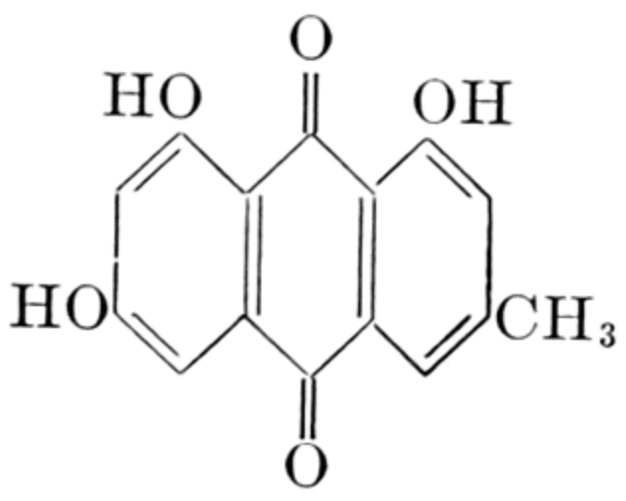


(XVII-10)

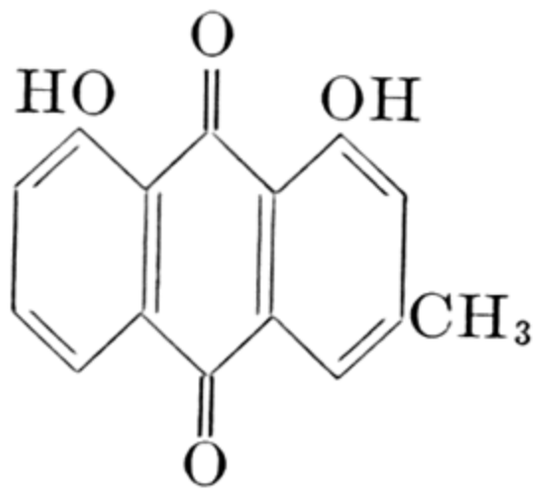
Aloe is a bitter tasting material consisting of the dried juice of the cactus-like leaves of African or Caribbean aloe plants. The active principles of aloe are mixtures known as aloin. The latter contains pentosides of anthraquinones and is often used in place of the viscous plant extracts. Aloin is hydrolyzed to its components in the intestines, and causes discomforting irritation as it induces peristaltic movements of the large bowel. The individual pentosides are barbaloin ($C_{20}H_{18}O_6$) which is hydrolyzed to aloe-emodin (XVII-9) and *D*-arabinose; isobarbaloin which gives 1,4,5-trihydroxy-2-methylanthraquinone (XVII-11) and an aldopentose; and β-barbaloin which furnishes another anthraquinone derivative.



(XVII-11)



(XVII-12)



(XVII-13)

Rhubarb is obtained from Chinese varieties of *Rheum* plants; the American varieties grown as vegetables are devoid of laxative action.

The cathartic principles of rhubarb are polyhydroxy-β-methylanthraquinones, and anthrapentosides.[10] Hydrolysis of the glycosides yields aloe-emodin (XVII-9), emodin (frangula emodin, 6-hydroxy-3-methyl-

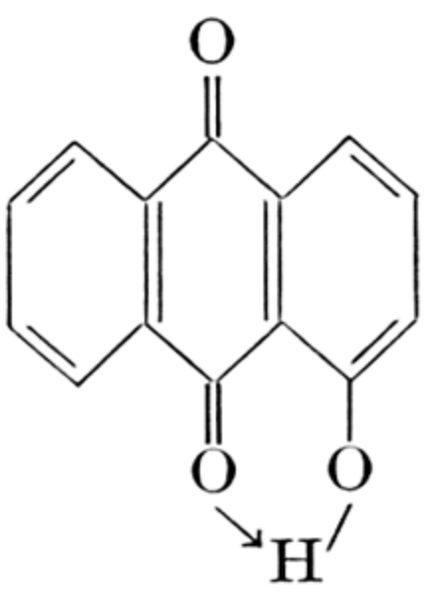
[9] Leger, *J. Pharm. Chim.* [7], **4,** 241 (1911). Oesterle, *Arch. Pharm.*, **250,** 301 (1912).
[10] Eder and Widmer, *Helv. Chim. Acta*, **6,** 966 (1923). Jacobson and Adams, *J. Am. Chem. Soc.* **46,** 1316 (1924).

chrysazin, XVII-12), emodin 6(?)-monomethyl ether, chrysophanic acid (3-methylchrysazin, XVII-13), rhein (XVII-10) and arabinose. The presence of tannins in rhubarb makes the drug constipating as well as laxative, and the constipation following administration of rhubarb preparations occasionally adds insult to injury.

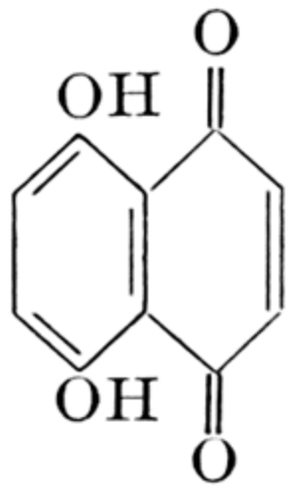
Cascara sagrada is the dried bark ("sacred bark") of the buckthorn (*Rhamnus purshiana*) which grows in the Western part of North America. The glycosides of this bark are frangulin which can be hydrolyzed to emodin (XVII-12) and an isomer, isoemodin. The plant also contains an emetic substance which slowly decomposes on storage, and this makes it imperative that the drug is not used within one year of its preparation.

The common feature of the 9,10-anthraquinones in these cathartic drugs is the presence of a methyl group or its oxidative stages (—CH_2OH, —COOH) in position 2, and at least two phenolic hydroxys in the 4- and 5- positions. Since aloe-emodin (with —CH_2OH) acts most powerfully, emodin and chrysophanic acid (with CH_3) less strongly and rhein (with COOH) least effectively, one must assume that the primary alcohol stage is distinguished by some special biological reactivity. One might compare this with the carcinogenic (also an irritant activity?) properties of 9-hydroxymethylbenzpyrenes which are more pronounced than those of the corresponding methyl derivatives.[11] The carboxyl group in rhein represents probably a partly detoxified—and therefore less active—stage of the anthraquinone cathartics.

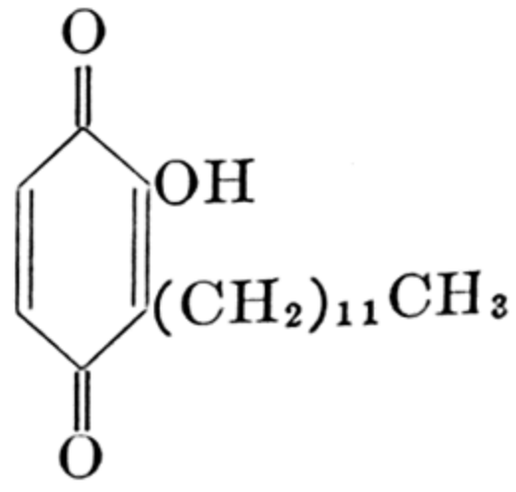
More important is the function of the alpha-hydroxyl group which, in the mordant anthraquinone dyes, can form chelated metal salts with the quinone carbonyl. It is interesting that all the hydroxyquinones known to possess cathartic activity contain phenolic hydroxyls in positions which permit chelation (XVII-14). This fundamental requirement is fulfilled in the different 1-hydroxyanthraquinones (1,2,7-, 1,2,6-, 1,2,3-, 1,2,4-trihydroxy-, 1,3-dihydroxy- and 1,2,3,4-tetrahydroxyanthraquinone) as well as in naphthazarin (XVII-15) and the *o*-hydroxy-*p*-quinone



(XVII-14)



(XVII-15)

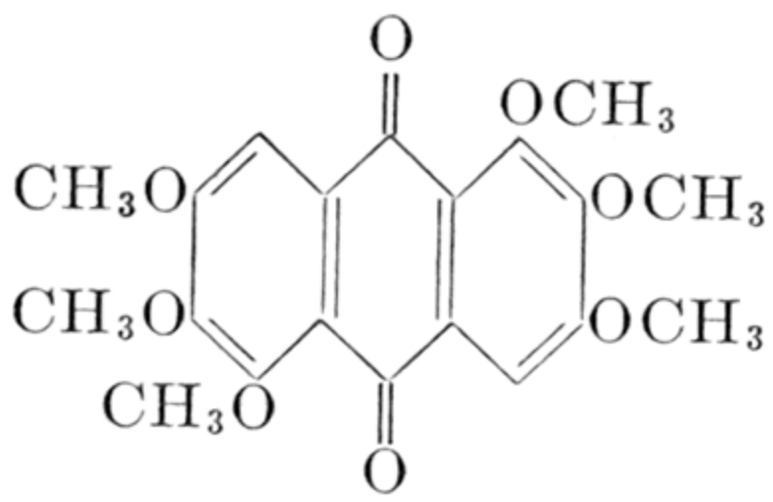


(XVII-16)

[11] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60,** 2542 (1938).

derivative, embelic acid[12] (XVII-16). As far as one can gather, hydroxyl groups other than those permitting chelation modify only the rate of absorption and alteration of the polyhydroxyanthraquinones in the intestine, and thus determine their ultimate cathartic usefulness in an indirect manner.

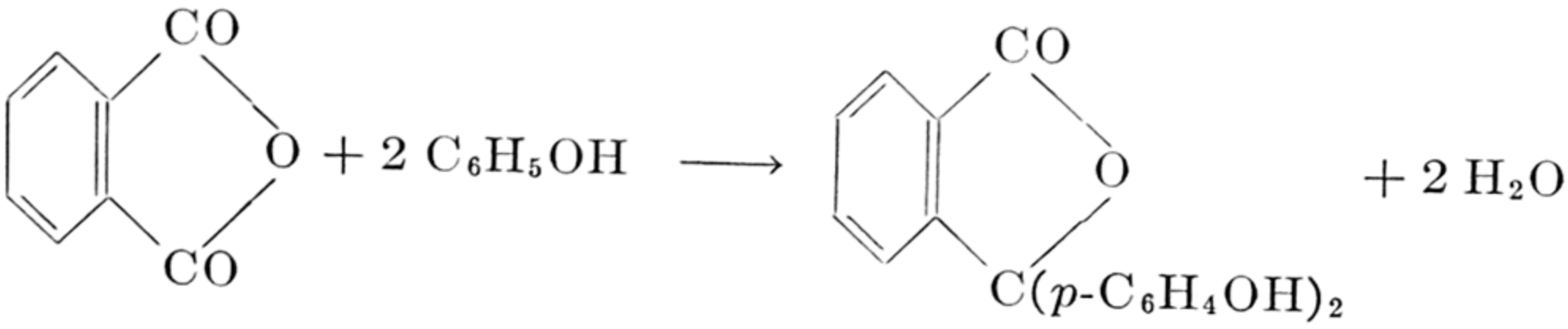
There have been numerous attempts to synthesize hydroxyquinones which would be pharmacologically superior to those obtainable from plant materials. Most of the synthetic analogs act, however, too drastically and also cause kidney damage. Only 1,8-dihydroxyanthraquinone (Istizin) and Exodin, the hexamethyl ether of rufigallic acid (XVII-17), have had short-lived practical use.[13]



(XVII-17)

b. Phenolphthalein

The laxative action of phenolphthalein (XVII-18) was discovered by accident when, about fifty years ago, the Hungarian government decreed that phenolphthalein should be added to wines to indicate contamination with basic adjuvants. The wines thus treated were then found to have cathartic effects. Phenolphthalein has become the most successful synthetic laxative, both because it is easily manufactured from phthalic anhydride and phenol, and because in contrast to many other laxatives.



(XVII-18)

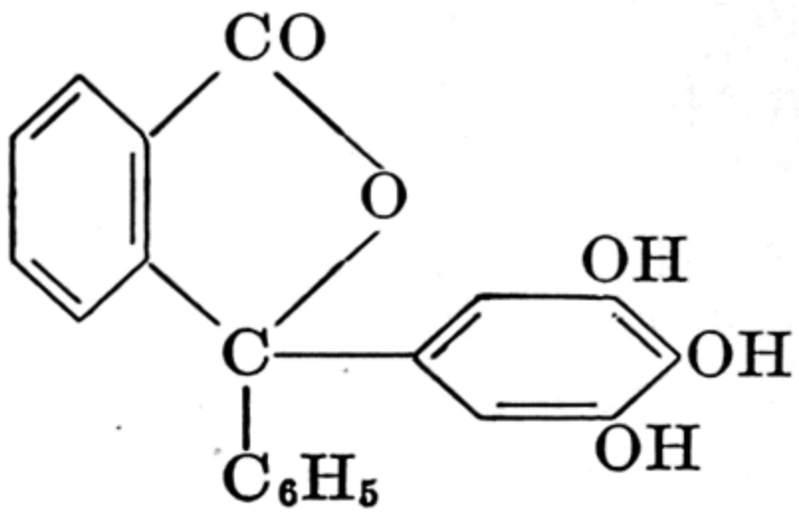
it does not damage the kidney. Pharmaceutical preparations containing phenolphthalein are on the market under countless names.

[12] Vieth, *Münch. med. Wochschr.*, **35,** 1381 (1901).

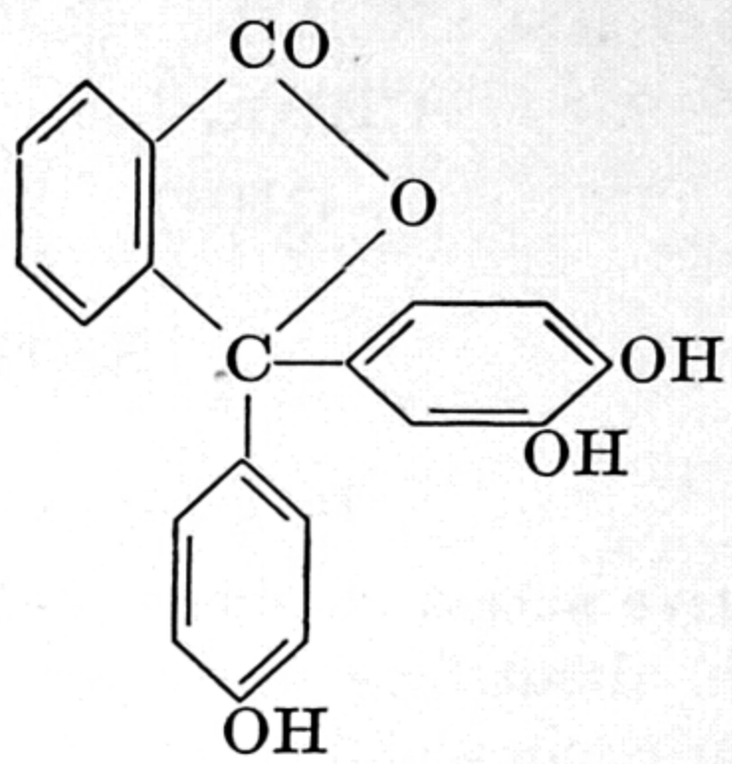
[13] Houben and Fischer, *Das Anthracen und die Anthrachinone,* Thieme, Leipzig, 1929. Fränkel, *Die Arzneimittel-Synthese*, 6th ed., Springer, Berlin, 1927, pp. 761–765.

The mechanism of the cathartic action of phenolphthalein has been the subject of much controversy in the pharmacological literature. The frequent statements that it acts as an intestinal irritant by virtue of its acidic phenolic groups can barely be taken seriously since many more acidic compounds, including phenolic analogs of phenolphthalein, possess no purgative properties. The question as to whether phenolphthalein acts locally on the smooth intestinal muscle, or by way of a nervous path, has not yet been answered.

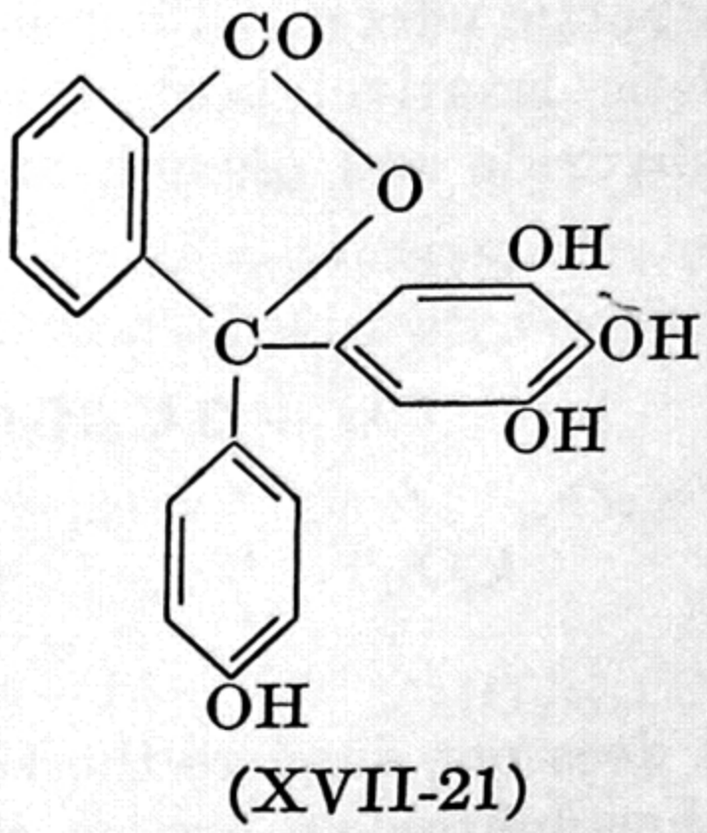
The effect of systematic variations of substituents in the phthalein structure and in related systems has been studied by Loewe.[14] Among polyhydroxy diphenylphthalides, the trihydric pyrogallolbenzenephthalein (XVII-19) has 1.63 times the laxophore activity of phenolphthalein. Phenolpyrocatecholphthalein (XVII-20) had 68.5%, and phenolpyrogallolphthalein (XVI-I21) 47% the potency of their prototype. Activity de-



(XVII-19)



(XVII-20)



(XVII-21)

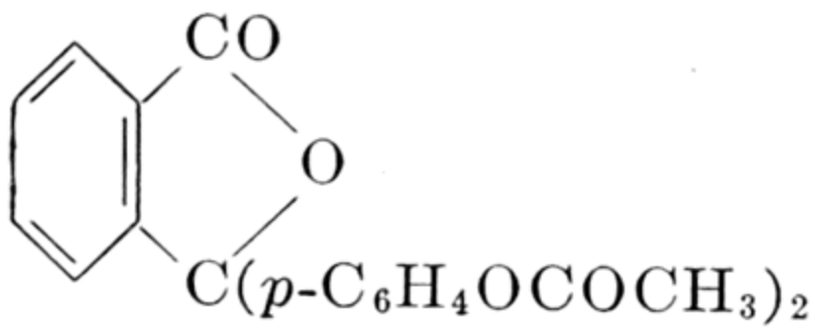
creased in general for less phenolic and non-phenolic phthaleins. Ethers and esters of the phenolic compounds were generally less active than the

[14] Loewe, *J. Pharmacol. Exptl. Therap.*, **94,** 228 (1948).

corresponding free phenols; for example, the diacetate and dibenzoate of phenolphthalein exhibited only 30%, and 8% respectively, of the laxative potency of their parent compound.

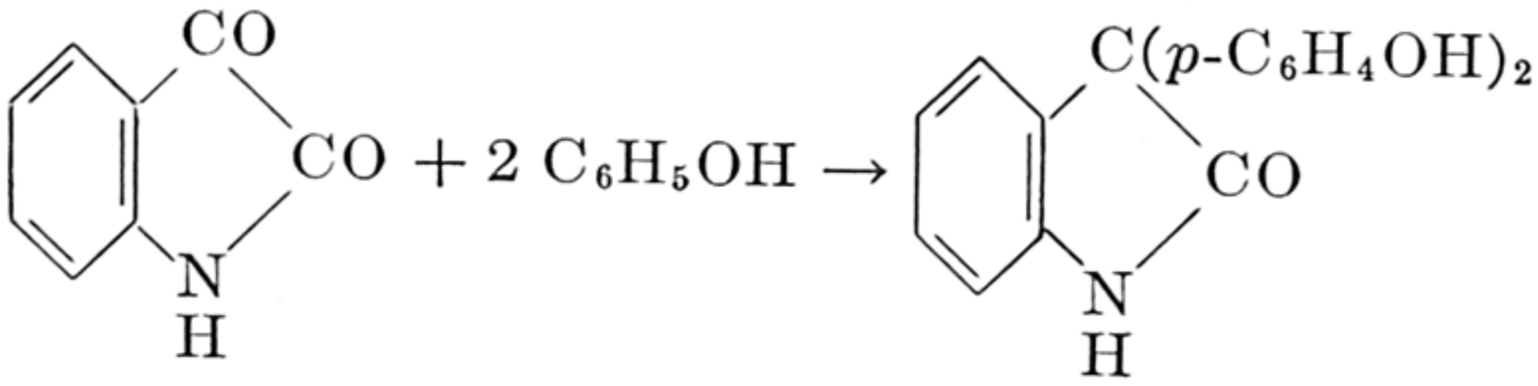
Among analogs of phenolphthalein, the laxophoric character of the two-ring system was lower in those derivatives in which the benzene part of the carbon structure was enlarged by substitution, or when the phthalide was replaced by phthalimide or anthrone. It was greatly enhanced in isatin or naphthalide structures. Phenolnaphthalein had five times the potency of phenolphthalein, and Isacen was 17 times more active (see below).

Some individuals are allergic to phenolphthalein but they usually have idiosyncrasies to other drugs as well. More common is the complaint that phenolphthalein causes intestinal griping, and this drawback can be overcome, in part, by using the diacetyl derivative (XVII-22). Other esters have also been tested; a mixture of the acetyl and isovaleryl derivatives has been marketed as Aperitol.

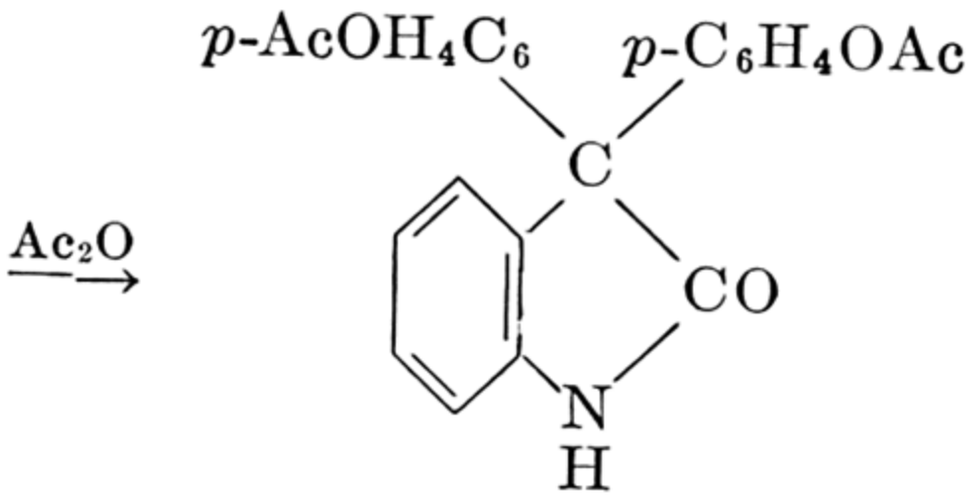


(XVII-22)

The lactam analog of diacetyl phenolphthalein, 3,3-bis-(*p*-acetoxyphenyl) oxindole (XVII-23) has been introduced as Isacen. It can be prepared by condensing isatin (XVII-24) with phenol and subsequently acetylating the hydroxyls of the reaction product.



(XVII-24)



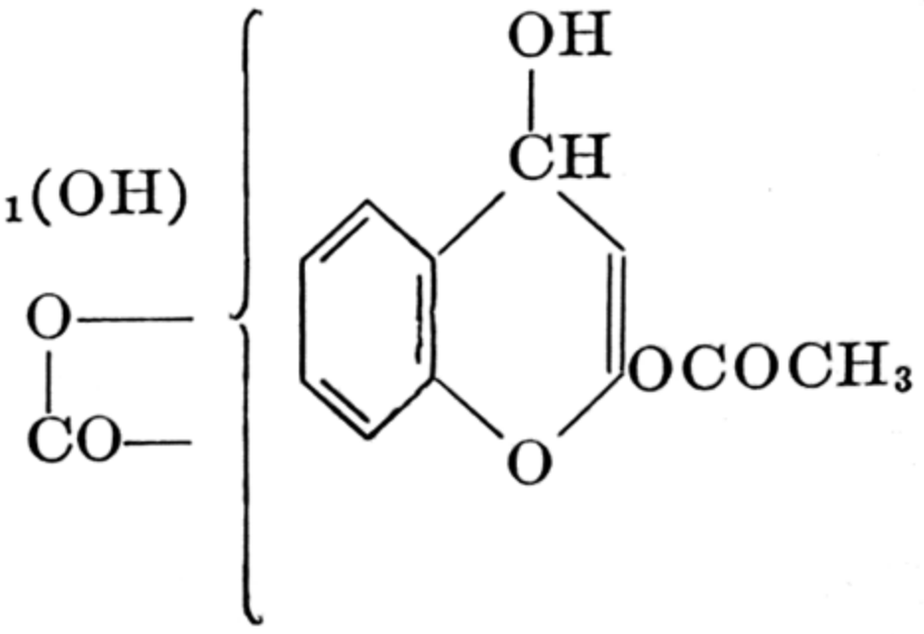
(XVII-23)

c. Cathartic Resins

The dried roots of plants of the *Convolvulaceae* family contain glucosidic resins which constitute ancient purgative medicines. From *Exogonium purga*, the resin convolvulin is obtained in Mexico, India and Jamaica. The jalap resin (jalapin) originates in *Ipomoea orizabensis*, while scammonin is a constituent of a resin from scammony found in a morning glory-like Mexican vine. The resins are insoluble in water but dissolve readily in bile or dilute solutions of bile salts. They have a marked solvent power for lecithins. The resins are also strongly hemolytic, and this property is retained to some extent by the glucosidic resin acids, purgic, convolvulic, jalapic and scammonic acids obtained by hydrolysis of the respective resins with barium hydroxide. Further hydrolysis with mineral acids splits off glucose and furnishes several alcoholic acids two of which have been characterized chemically.[15] Jalapinolic acid is (+) 11-hydroxyhexadecanoic acid [$CH_3(CH_2)_4CHOH(CH_2)_9CO_2H$], while convolvulinolic acid is a hydroxypentadecanoic acid; the position of the alcoholic hydroxyl group of this compound has not been definitely determined.

The structural analogy between these hydroxy acids and the much more carefully investigated ricinoleic acid from castor oil is unmistakeable. It is possible that all these acids owe their cathartic activity to their ability to detach a protective lecithin film from the intestinal wall.[16]

The Mediterranean curcubitacea, *Ecballium elaterium* (bitter apple, bitter cucumber), a water melon-like plant, contains in the pulp of its unripe fruit an intestinally irritant resin called colocynth. Several phytosterols have been isolated from this fruit, but the drastic cathartic and diuretic action of the resin appears to be due to two optically active compounds, alpha- and beta-elaterin. The laevorotatory alpha-derivative



(XVII-25)

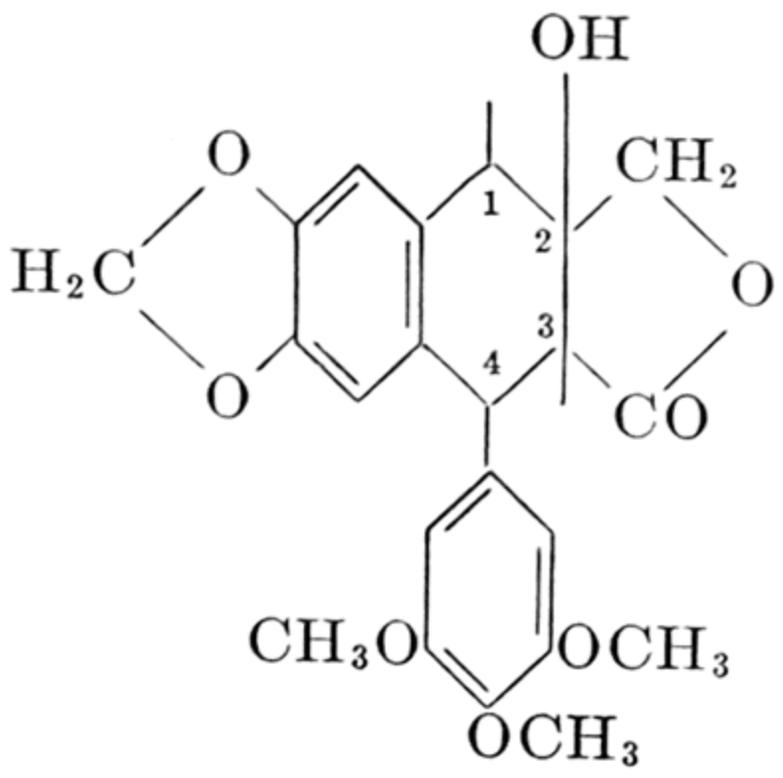
[15] Davies and Adams, *J. Am. Chem. Soc.*, **50,** 1749 (1928).
[16] Valette, *Compt. rend. soc. biol.*, **125,** 405 (1937).

has been the subject of a preliminary structural study.[17] It has the composition $C_{28}H_{38}O_7$ and contains a benzopyrone ring system. A provisional formula can be expressed by (XVII-25).

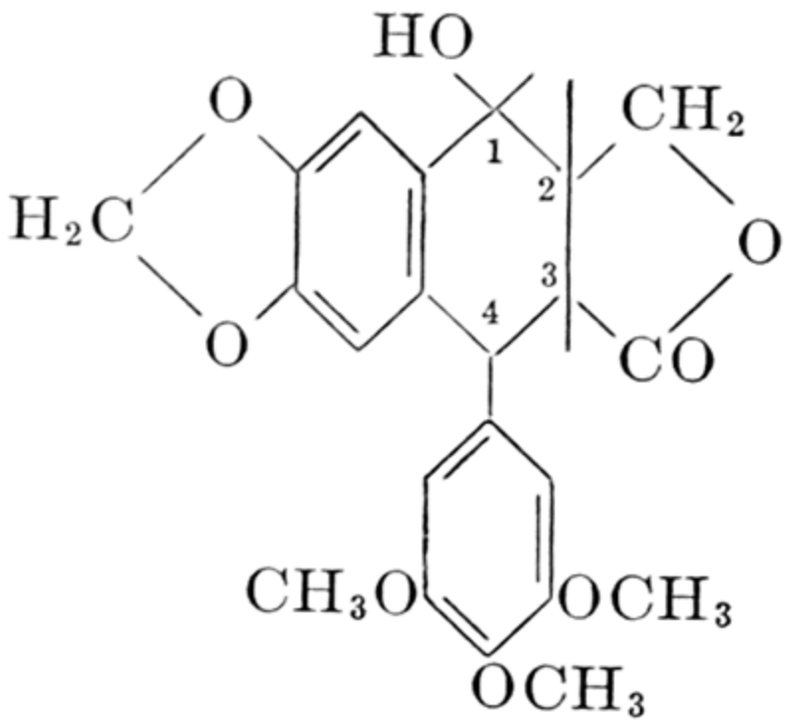
d. Podophyllum

The dried rhizomes and roots of certain *Berberidaceae* yield resinous mixtures which have both medicinal and poisonous properties. The most common source of these resins is *Podophyllum peltatum*, also called may-apple root or mandrake apple. It grows in the Northeastern United States and in Canada, and its podophyllum resin was used by American Indians as an anthelmintic, emetic and cathartic. A similar resin is obtained by alcohol extraction of the North-Indian *Podophyllum emodi*.

The crude resins contain toxic materials which can be removed by extraction with chloroform.[18] The purified resins from both sources owe their physiological activity principally to podophyllotoxin. This is accompanied by a pharmacologically inert isomer, picropodophyllin, $C_{23}H_{24}O_9$, and by the yellow hydroxyflavone, quercetin or podophyllo-quercetin.[19] The structures of the isomeric compounds have been elaborated by Borsche and Niemann, and by Hartwell.[20] In contrast to older proposed structures, podophyllotoxin and picropodophyllin appear to be C_3-epimers as expressed by the alternative formulas (XVII-26) and (XVII-27). The position of the hydroxyl group has not yet been definitely located.



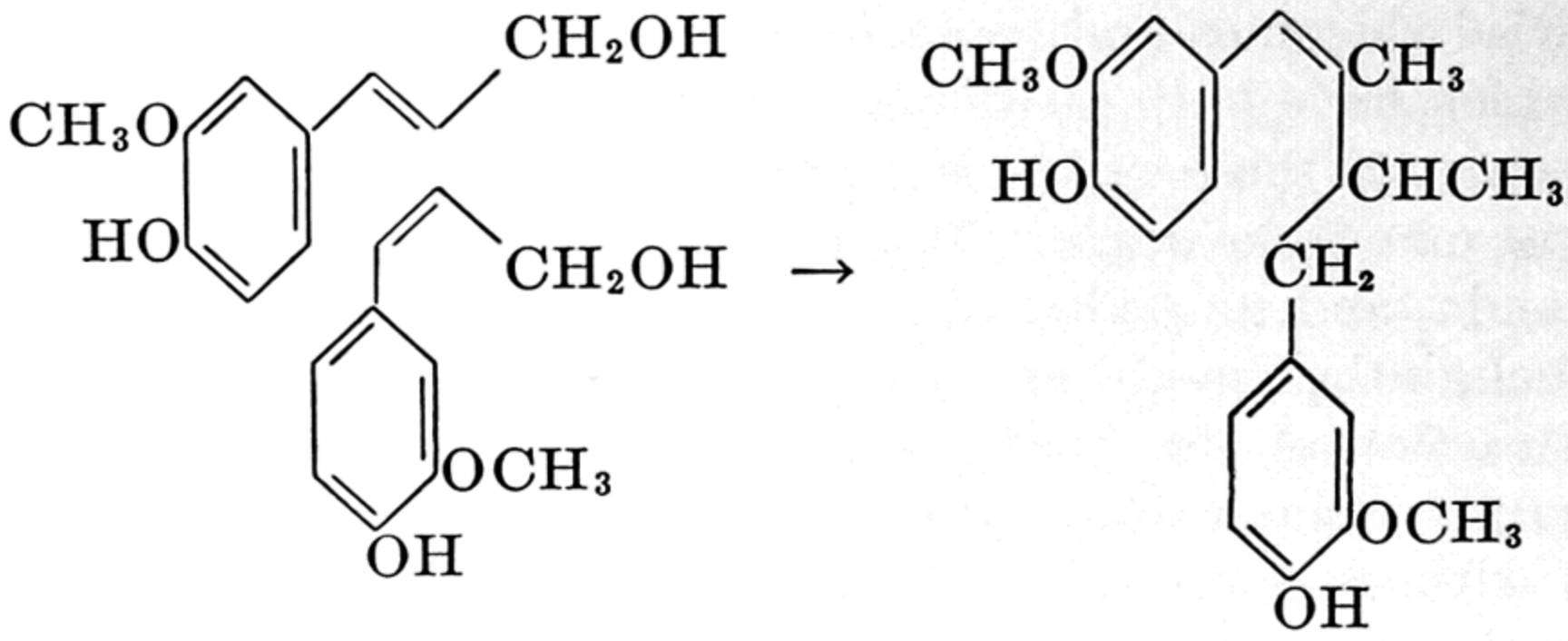
(XVII-26)



(XVII-27)

[17] Borsche and Diacont, *Ann.*, **528,** 39 (1937).
[18] Viehover and Mark, *J. Am. Pharm. Assoc.*, **27,** 632 (1938).
[19] Dunstan and Henry, *J. Chem. Soc.*, **73,** 209 (1898).
[20] Borsche and Niemann, *Ann.*, **494,** 126 (1932); **499,** 59 (1932), Borsche, *Ann.*, **526,** 1 (1936). Hartwell and Schrecker, *Abstracts*, Meeting Am. Chem. Soc., Philadelphia, Pa., April 10, 1950, p. 3K.

The structures expressed by (XVII-26) and (XVII-27) bear a certain resemblance to guaiac resin acid[21] (XVII-28) which probably arises from the condensation of two molecules of coniferyl alcohol (XVII-29). This similarity sheds some light on the natural origin of the podophyllum



(XVII-29) (XVII-28)

substances. The diphenylmethane portion, and the presence of a lactone ring in podophyllotoxin also recall similar structural characteristics of the phenolphthalein molecule and suggest a relation of these groups to gastrointestinal activity.

e. Irritant Cathartic Oils

Extraction of the castor bean, the seed of *Ricinus communis*, furnishes a colorless and—when pure—tasteless oil which has been used for generations as a purgative under the name of castor oil. Its medicinal use has declined somewhat in recent years and new outlets for this important agricultural product have been found by incorporating it in hair tonics, and using it as a raw material in the plastics industry.

The essential acyl components of castor oil are ricinoleic acid (12-hydroxy-9-octadecenoic acid, $CH_3(CH_2)_5CHOHCH_2CH = CH(CH_2)_7COOH$), accompanied by smaller amounts of its stereoisomer, isoricinoleic acid, and 9,10-dihydroxystearic acid. Isoricinoleic acid can be formed by acid rearrangement of ricinoleic acid. It is inactive, and its esters do not produce catharsis either. The burden of the laxative activity of the oil rests on ricinoleic acid. Synthetic derivatives from which the acid can be regenerated in the intestine are active, whereas insoluble salts, amides, etc. have no laxative properties. Local irritation in the small intestine, perhaps by a de-lecithinizing of the mucosa, is responsible for the action of ricinoleic acid.

Esterification of the alcoholic groups of ricinoleic acid with benzoyl, anisyl and other acyl groups has been undertaken in the hope of decreas-

[21] Schroeter, Lichtenstadt, and Irineu, *Ber.*, **51**, 1587 (1919).

ing the nauseating side-effects especially of cruder castor oil preparations. These acyl derivatives have not become useful laxatives.

A now virtually abandoned purgative is croton oil, obtained from the seeds of *Croton tiglium*. It is the most drastic cathartic and so irritant that doses of 0.05 g. will bring about extensive evacuation. The oil contains an irritant crystalline alcohol, phorbol, which acts not only in the intestine but can be used as a blistering agent and counter irritant on the skin.

Sodium ricinoleate has also found use in sclerosing varicose veins. In such veins it is necessary to produce a firm and adherent thrombus and then to protect it from excessive hydrostatic pressure for a long time. Other salts of long-chain acids have also been employed, for example, sodium 2-methyl-7-ethylundecyl-4-sulfate $[CH_3(CH_2)_3CH(C_2H_5)(CH_2)_2 CH(OSO_3Na)CH_2CH(CH_3)_2]$.

VIII. EMETICS

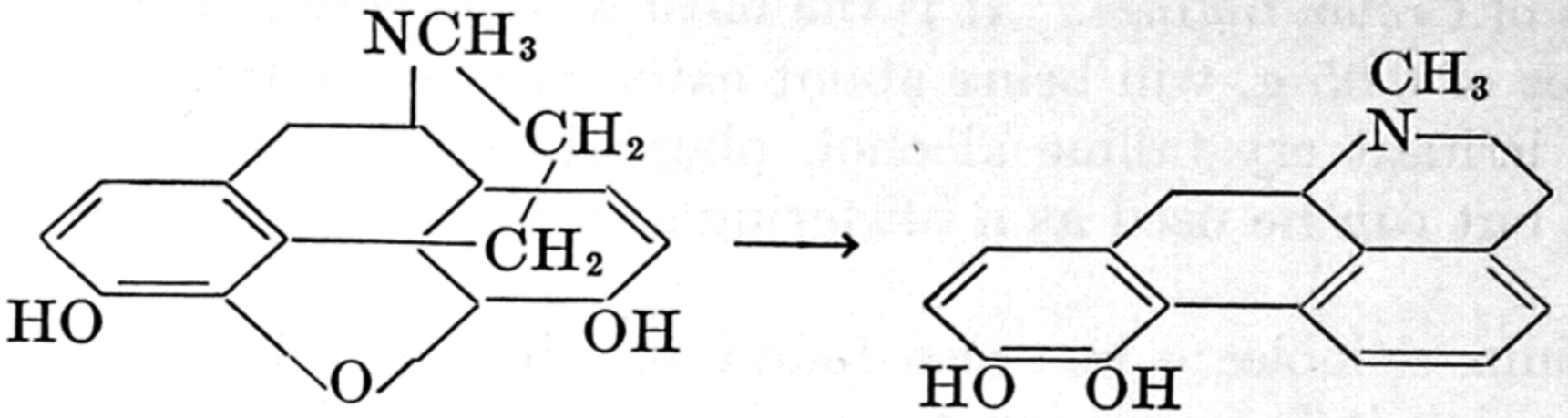
Emetics are drugs which induce vomiting. They have been used in cases of food or drug poisoning, or to remove foreign objects from the stomach, but are being employed rarely now and have been superseded by lavage of the stomach through the stomach tube. It is a dubious compliment for a drug to be labeled an emetic: on the whole, emesis is a toxic side-effect that only too many chemicals produce.

Vomiting is a complicated act arising from the confluence of many organic and psychic factors. Some compounds appear to cause emesis by peripheral nervous mechanisms, by action on the heart, or reflexly by local irritation of the gastric mucosa, but the majority of emetics act upon the vomiting center in the medulla. Their effect can still be noted in the retching movements and the nausea of laboratory animals whose gastro-intestinal organs have been completely excised.

Copper sulfate, zinc sulfate and potassium-antimony tartrate (Tartar Emetic) have been employed as peripherally acting emetics but their margin of safety is small. The active irritant principle of mustard, allyl isothiocyanate ($CH_2{=}CHCH_2NCS$) also causes emesis by reflex action after local irritation. An as yet uncharacterized lobelia alkaloid,[22] and the alkaloids sempervirine and gelsemoidine from *Gelsemium*[23] also belong in this group. Indeed, the alkaloid emetine, the chief base of ipecac, has a peripheral component in its emetic action although it acts mainly by a central mechanism. Its unsafe emetic and nauseant properties limit the decidedly effective application of emetine as an amebicidal agent (Chapter XXXVII).

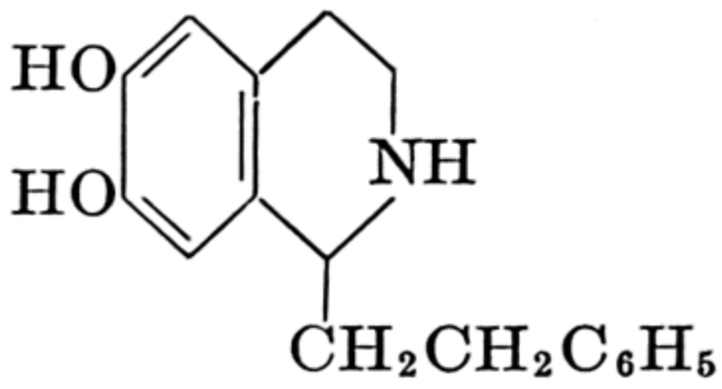
[22] Richter, *Arch. exptl. Path. Pharmakol.*, **193,** 117 (1939).
[23] Christensen and Gramling, *J. Am. Pharm. Assoc.*, **27,** 1208 (1938).

The most important centrally acting emetic is apomorphine (XVII-30), obtainable from morphine (XVII-31) by treatment with hot mineral acids. The rearrangement of the N-heterocyclic section, and the disappearance of the furanoid ether ring bring about a deep change in pharmacological behavior. Apomorphine no longer has analgetic properties but its excitatory action on the vomiting center has become predominant.



(XVII-31) (XVII-30)

As pointed out in the discussion of opium alkaloids, morphine and many of its semi-synthetic derivatives cause nausea and vomiting in a considerable number of individuals. Other isoquinoline derivatives have similar properties. For instance, analgetic and emetic action has been claimed for 1-phenethyltetrahydroisoquinoline derivatives such as (XVII-32).[24]



(XVII-32)

A rather unexpected emetic effect can be produced by intravenous infusion of glutamic acid, $HO_2CCH(NH_2)(CH_2)_2CO_2H$. The implication of this observation for the clinical use of protein hydrolysates is not clear.[25]

IX. ANTI-EMETICS

Emetic spasms can be combatted by hypnotics and sedatives which lower the excitation of the vomiting center. Nembutal and other barbiturates are quite effective.

The nausea and emesis of motion sickness, of pregnancy and of post-anesthetic conditions can be overcome successfully by Dramamine, the 8-chlorotheophyllinate of Benadryl. The chemistry of this drug will be described in Chapter XXIV.

[24] Külz and Hornung, U. S. Pat. 2,223,373 (1939).
[25] Roth, Richards, and Steggerda, *Proc. Soc. Exptl. Biol. Med.*, **62,** 282 (1946).

CHAPTER XVIII

Expectorants

Expectorants are drugs which relieve congestion in the lower respiratory tract, the lungs, bronchi and trachea, by removing mucous exudates from inflamed surfaces of these organs. The usual method of evaluating expectorant activity is to collect the fluids expelled from the respiratory tract by coughing, and measuring their volume.[1] The mechanism by which expectorants act determines their traditional classification[2] as sedative, anodyne and stimulant expectorants.

I. SEDATIVE EXPECTORANTS

Sedative expectorants aid in the secretion of a protective mucous film which covers up inflamed membranes and increases the efficiency of the removal of slimy exudates by coughing. A number of simple salts have proved their value for this purpose. Ammonium carbonate, chloride, and acetate, alkali citrates, and especially inorganic iodides are widely used. The latter, taken orally or intravenously, are excreted into the bronchial secretion within 15 to 25 minutes, and their irritating action there accounts perhaps for their expectorant activity.[3]

Small doses of tartar emetic (antimony potassium tartrate) have long been used to loosen mucus in the respiratory organs. Ipecac, the parent material of emetine, mixed with sweet-tasting syrups, is one of the favorite expectorants in croupous bronchitis in children. These substances are classified as nauseating sedative expectorants. Their syrupy pharmaceutical preparations also contribute to a soothing action on irritated membranes of the throat. This result is achieved even more effectively by the so-called demulcent syrups of *Acacia* and the like.

The alkaloid thermopsin from *Thermopsis lancelolata* is said to be more effective than ipecac as an expectorant in tuberculosis. It acts as a nauseating irritant but has also a central effect on the respiratory and vascular centers.[4]

[1] Perry and Boyd, *J. Pharmacol. Exptl. Therap.*, **73,** 65 (1941).
[2] Brown, *J. Am. Med. Assoc.*, **109,** 268 (1937). Green, *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **4,** 377 (1943).
[3] Tuft and Levin, *Am. J. Med. Sci.*, **203,** 717 (1942).
[4] Kalashnikov and Kuznetsov, *Farmatsiya i Farmakol.*, **1937,** No. 7, 1; *Chem. Abstr.*, **33,** 7490[5] (1939).

II. ANODYNE EXPECTORANTS

Anodyne expectorants act by depressing the area in the central nervous system which controls the cough reflex. The opium alkaloids codeine and—to some extent—morphine, as well as the semi-synthetic morphine derivatives, Dicodid and Dilaudid, act by this mechanism. Codeine is probably the most effective and most widely used of these substances and constitutes the main antitussive component of many cough syrups. These mixtures have the purpose of stimulating secretion of mucus and yet delaying cough until the mucus can be expelled.

The chemistry of the opiates has been discussed in Chapter XI.

There is much evidence for the theory that morphine and its derivatives act partly by an autonomic mechanism. Part of the parasympathetic syndrome is a profuse stimulation of secretions of glands and membranes. The cholinergic drugs (acetylcholine, Urocholine, Furmethide, Prostigmin, etc.) also increase the output of fluid from the respiratory tract to over 1000% and may therefore be useful in expectorant medication.[5]

By opposite reasoning, substances which suppress mucous secretions in the lower respiratory tract should alleviate congestion in these organs; the adrenergic drugs, epinephrine and ephedrine have actually been found of value in this respect.

III. STIMULANT EXPECTORANTS

The so-called stimulant expectorants comprise two groups, the mildly irritant volatile terpenoid oils, and the phenolic materials based on creosote which are excreted partly through the lungs and stimulate healing processes in inflamed areas of the bronchies.

1. Terpenoid Oils

The most common terpenoid oils which possess expectorant properties are oil of turpentine, pine, juniper, lemon, eucalyptus, and oil of anise. The latter is the most effective of this group. In addition, terpin hydrate (XVIII-1) and cineol (XVIII-2) are useful expectorants.[6] The mechanism of their irritant and healing action has not been studied adequately. The whole field of using terpenes as medicinals has been neglected, in spite of the fact that so many pharmaceutical syrups and oils contain terpene components as flavoring agents.

Oil of turpentine is obtained by steam distillation of the turpentine resin which is excreted through incisions made in the bark of coniferous trees, especially pines. The residue from the steam distillation contains

[5] Boyd and Lapp, *J. Pharmacol. Exptl. Therap.*, **87,** 24 (1946).
[6] Boyd and Pearson, *Am. J. Med. Sci.*, **211,** 602 (1946).

rosin (Colophonium) which is used in the lacquer, electrical, tar and paper industries. It consists of polymeric anhydrides of abietic acid and similar products.

The main constituent of oil of turpentine is α-pinene (XVIII-3). It is usually accompanied by the isomeric β-pinene (XVIII-4) in which the

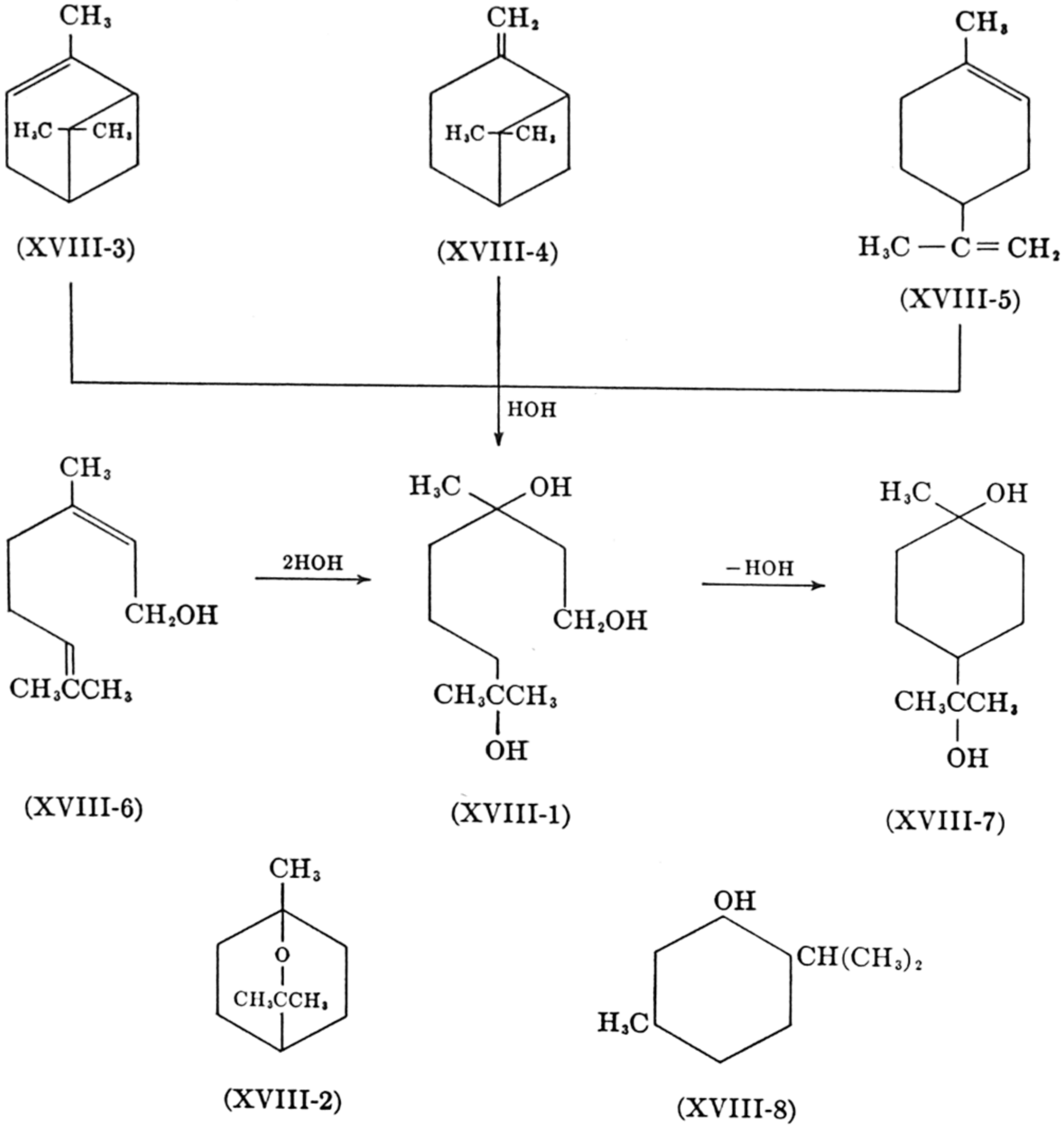


Figure 1. Terpenoid Oils

double bond is extracyclic. α-Pinene is also found in other essential oils, for example, in oil of lemon, in which it occurs in smaller quantities besides dextro-limonene (XVIII-5), the main constituent of this oil. Dipentene (XVIII-5) is DL-limonene and occurs in *oleum cinae* besides cineol (eucalyptol, XVIII-2).

When a mixture of pinenes from oil of turpentine is treated with dilute mineral acids at ordinary temperature for some time, the triol terpin hydrate (XVIII-1) is obtained by hydration. The latter can also be synthesized in a more clear-cut manner from geraniol (XVIII-6) by a similar process. Continued heating at 100° dehydrates terpin hydrate to the cyclic diol, terpin (XVIII-7).

Cineol (XVII-2) is the main constituent of oil of Eucalyptus, obtained by steam distillation of the leaves of the tree, *Eucalyptus globulus*. Other essential oils, (wormseed, rosemary) also contain cineol. Chemically, cineol can be regarded as an inner ether of terpin.

Mention should be made of the very common incorporation of the active principles of other essential oils in cough medicines. Menthol, eugenol and isoeugenol are frequent components of cough drops, lozenges, inhalers and externally irritant ointments. Menthol (XVIII-8) is the essential constituent of oil of peppermint from which it crystallizes on cooling. The major portion of commercial menthol is now manufactured synthetically.

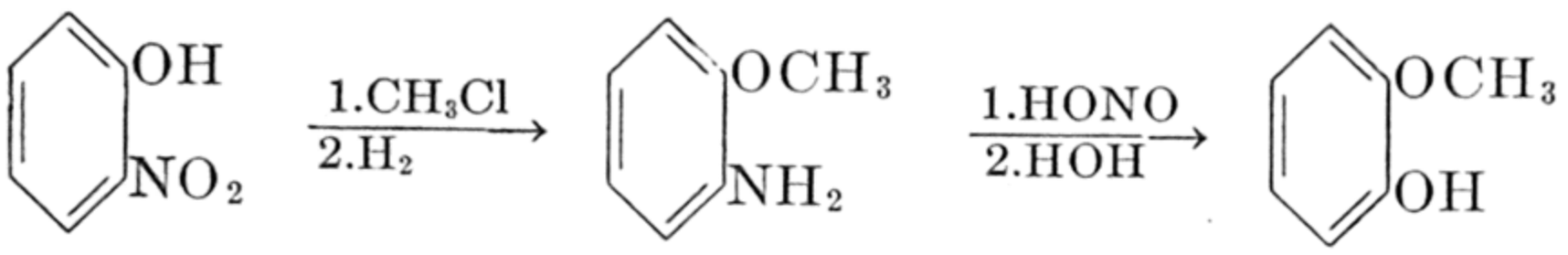
2. Creosote, Guaiacol and Creosol

Creosote is a mixture of phenols derived from wood tar. Its main source is beechwood, but birch-, pine- and oakwood also furnish Creosote on pyrolysis. The smoky odor and sharp taste of Creosote is encountered again in its phenolic constituents, phenol, cresol, dimethylpyrogallol and the active principles of the oil, guaiacol (2-methoxyphenol), and creosol (2-methoxy-4-methylphenol). These phenols, expecially guaiacol, are part of many mixtures used as stimulant expectorants. They are of definite value in loosening mucus with special application to chronic inflammatory processes such as bronchitis, lung abscesses or tuberculosis. The sputum decreases in quantity and loses its foul taste. There is no scientific support for the old claim that guaiacol has curative properties in tuberculosis. The antiseptic power of guaiacol is negligible, its phenol coefficient low, and any relief obtained from its use is purely symptomatic.[7]

Creosote has been used in inhalers and as an adjuvant to steam inhalation in sick rooms. The calcium salts of the active phenols, calcium creosotate, can be taken orally, as can be creosote carbonate, prepared from Creosote and phosgene. In recent years, pure guaiacol has partly superseded Creosote, and most of the chemical work on stimulant expectorants in this group has been based on guaiacol.

[7] Fellows, *Am. J. Med. Sci.*, **197,** 683 (1939); Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **110,** 209 (1938).

Guaiacol (XVIII-9) is manufactured from *o*-nitrophenol which is methylated with methyl chloride and reduced to *o*-anisidine. The latter is diazotized, and the diazo solution is hydrolyzed with an acid solution of copper sulfate.



(XVIII-9)

Efforts to improve upon guaiacol stem from the relatively high systemic toxicity, the locally irritant action, the low solubility in water, and the bad taste of the parent compound. Numerous derivatives designed to overcome these drawbacks have been tested, and have been used occasionally, but none of them are superior to guaiacol in all ways.

The burning taste of guaiacol is lost in its phenolic esters, but the elimination of the hydroxyl function in these compounds decreases their solubility in water. The first ester which was introduced into therapy was guaiacol carbonate (Duotal, XVIII-10) which was prepared by the action of phosgene or ethyl chlorocarbonate upon sodium guaiacolate.

(a) $2\ CH_3OC_6H_4ONa + COCl_2 \rightarrow (CH_3OC_6H_4O)_2CO + 2\ HCl$

(b) $2\ CH_3OC_6H_4ONa + ClCOOC_2H_5 \rightarrow (CH_3OC_6H_4O)_2CO$
(XVIII-10) $+ NaCl + NaOC_2H_5$

Inorganic esters of guaiacol were prepared with the anticipation that—as in guaiacol carbonate—they would be hydrolyzed in the body to guaiacol and a physiologically inert acid component. The phosphate (XVIII-11) can be made from the phenol and phosphorus oxychloride.

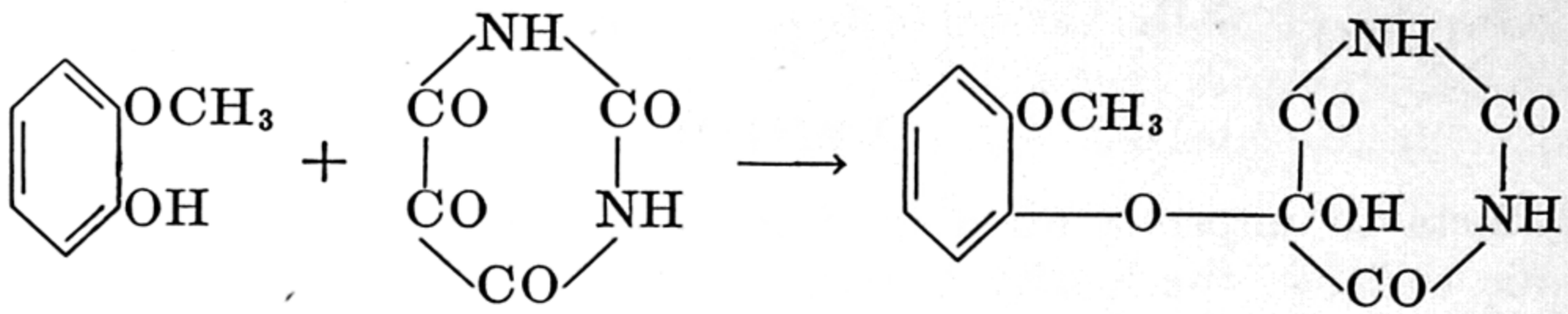
$$3\ CH_3OC_6H_4OH + POCl_3 \rightarrow (CH_3OC_6H_4O)_3PO + 3\ HCl$$
(XVIII-11)

Guaiacol acetate, valerate, cinnamate, etc., have also been tested. The main advantage of the more complex esters is their increased solubility in lipids which gives an altered distribution picture in different organs. Some of them appear to exert an antiseptic action without being hydrolyzed to the components.

Ethers of guaiacol are of interest only as far as the ether group introduces new hydrophilic functions. The glyceryl ether, *o*-$CH_3OC_6H_4$-$OCH_2CHOHCH_2OH$, is water-soluble and has expectorant properties similar to guaiacol; it has been said to be cleaved to its components by the intestinal flora. In any case, the bad taste of the parent compound re-

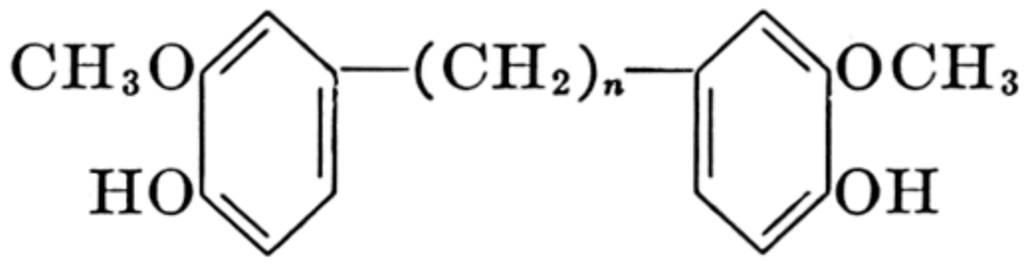
turns with solubility in water, and the compound has no advantages over guaiacol.

A tasteless and water-soluble derivative of guaiacol which is hydrolyzable to its components can be obtained by addition of alloxan (XVIII-13) to guaiacol. The addition product (XVIII-12) is, however, as toxic as the parent phenol.



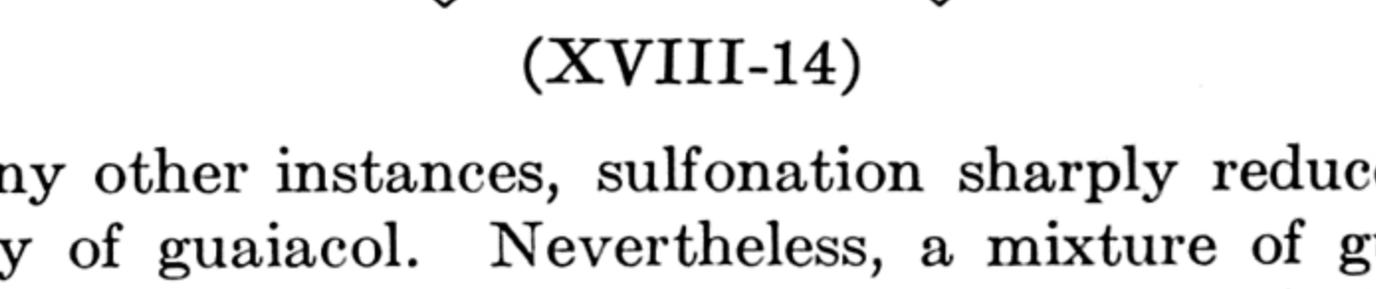
(XVIII-13) (XVIII-12)

No advantages are gained by condensing guaiacol with formaldehyde (XVIII-14, $n = 1$) or separating the two aromatic rings by a polymethylene chain (XVIII-14, $n > 1$). These compounds are as irritating as guaiacol and less active. Replacement of the methoxyl group of guaiacol by ethoxyl does not alter its properties.



(XVIII-14)

As in many other instances, sulfonation sharply reduces the physiological activity of guaiacol. Nevertheless, a mixture of guaiacol-4- and -5-sulfonic acids has been used for years under the name of Thiokol (XVIII-15). The solubility of the sodium or triethanolammonium salts of these acids is high, but their activity is doubtful. Similar sulfonic acids derived from thymol (XVIII-16) have been recommended even in more recent years.[8] Thymol is manufactured from oil of thyme or oil of ajowan (from *Ptychotis coptica*), and can be used as a relatively non-toxic, insoluble,



(XVIII-15) (XVIII-16)

and systemically poorly absorbed antiseptic agent.

[8] Goebel, German Pat. 672,857 (1939).

CHAPTER XIX

Adrenergic Drugs

I. INTRODUCTION TO AUTONOMIC DRUGS

This Chapter and the following four deal with drugs acting on cell chemicals of organs and muscles innervated by autonomic nerves. The most prominent compounds in this group have been classified as adrenergic and cholinergic stimulants and blocking agents. An understanding of their classification and pharmacodynamic differences is based on the mode of transmission of nervous impulses, and on a brief survey of the anatomy and physiology of the autonomic (vegetative or involuntary) nervous system.

1. The Autonomic Nerves

The secretory power of the glands, the involuntary movements of the smooth muscles, the viscera, the heart and the blood vessels are regulated by the autonomic nerves. The somatic nerves, by contrast, control the voluntary skeletal muscles. The functions of both nervous systems, the involuntary and the somatic, are integrated in the central nervous system to permit smooth operation, and coordination of all body functions.

The two motoric branches of the autonomic nervous system are the sympathetic and the parasympathetic divisions. The sympathetic nerve cells, lying in the so-called sympathetic chain emanating from the spinal cord, are connected with axones which synapse with neurons but often not before traversing several other ganglia. The neurons at which the synapse occurs lie in terminal ganglia sometimes at a considerable distance from the innervated organ. This, together with the great ramification of sympathetic nerves, may cause synapsing of one preganglionic fiber with many postganglionic neurons. The preganglionic fiber resembles the main wire from a switchboard which is subdivided into many party lines. Just as one can listen to a conversation of another party on the same line, impulses received from, or transmitted to any given effector organ (glands, muscles) will also be felt by other organs innervated by sympathetic nerves. At times of great stress all these organs are mobilized simultaneously for the defense of the whole body, the sympathetic nervous system acting as a unit. Drugs which mimic sympathetic stimulation will therefore have effects in many parts of the organism.

The long preganglionic fibers of the parasympathetic nerves emerge from the central nervous system, the brain, the medulla oblongata and the

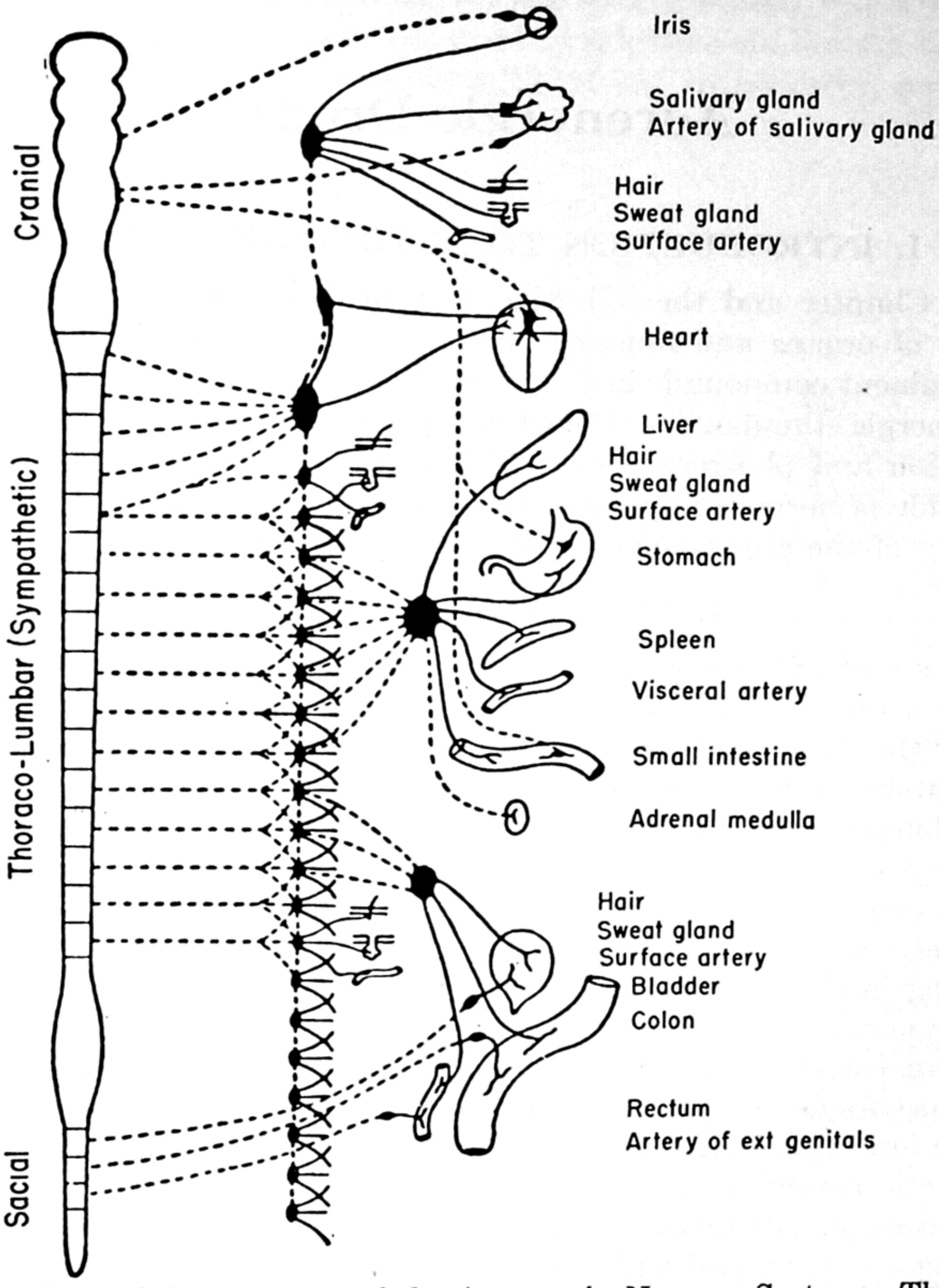


Figure 1. General Arrangement of the Autonomic Nervous System: The central nervous system is represented at the left. Somatic nerves are not shown. The preganglionic fibers are in broken lines, the postganglionic fibers in solid lines.*

sacral part (the four lowest segments) of the spinal cord. They connect to short postganglionic portions innervating glands, viscera, sex organs,

*From Murchison, *Foundation of Experimental Psychology*, Clark University Press, Worcester, 1929.

the iris, etc. The terminal parasympathetic ganglia lie near these organs, and therefore each innervated organ can be stimulated separately with relatively little effect on the other body structures connected to this system. The heart may be slowed by parasympathetic stimulation, or by parasympathomimetic drugs without a lowering of the blood pressure; or the bladder and the rectum can be emptied without an effect on vision. The parasympathetic nerves (cranial, facial, vagus, sacral) thus elicit distinct and separate symptoms in remote locations of the body. Vasodilator control is a function of the parasympathetic system.

Virtually every involuntary muscle or gland cell is innervated by both sympathetic and parasympathetic fibers. One may therefore observe the effects of either stimulation or blocking in the same organ. Some organs can exhibit an automatic (autonomous) activity even if denervated. The effects of exciting and depressing the involuntary muscles and the glands can be demonstrated best on organs removed from the body. For instance, spasms of isolated visceral muscles can be allayed by certain antispasmodics which act directly upon the surviving organ irrespective of innervation (musculotropic drugs). Other compounds producing similar gross effects act directly on the nerve (neurotropic drugs) and by means of this mechanism finally upon the innervated end-organs.

2. Acetylcholine

Definite proof for chemical mediation of nervous transmission was advanced by the classical researches of Loewi,[1] of Dale,[2] and of Cannon.[3] Loewi stimulated the vagus nerve of a surviving frog heart (donor) suspended in a buffered isotonic salt solution; a substance which he called vagus substance or parasympathin was liberated into the perfusion liquid, and the rate of a second frog heart (recipient) could be slowed down by it. Later evidence established the fact that parasympathin is really acetylcholine ($CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3\overset{-}{O}H$).

Acetylcholine is released from an inert precursor of unknown nature at the synapse by *pre*ganglionic nerve impulses in any part of the nervous system, sympathetic or parasympathetic. These impulses stimulate ganglionic cells. It will be seen that this theory, together with that concerning sympathin, has made necessary a reclassification of nervous functions. Any nerve which releases acetylcholine to effector organs is now called

[1] Loewi, *Arch. ges. Physiol.*, **189,** 239 (1921).

[2] Dale, *J. Pharmacol. Exptl. Therap.*, **6,** 147 (1914). Dale and Gasser, *ibid.*, **29,** 53 (1926). Dale and Feldberg, *J. Physiol.*, **81,** 320 (1934); **82,** 121 (1934); **86,** 353 (1936).

[3] Cannon and Uridil, *Am. J. Physiol.*, **58,** 353 (1921). Cannon and Rosenblueth, *ibid.*, **104,** 557 (1933). Cannon and Lissak, *ibid.*, **125,** 765 (1939).

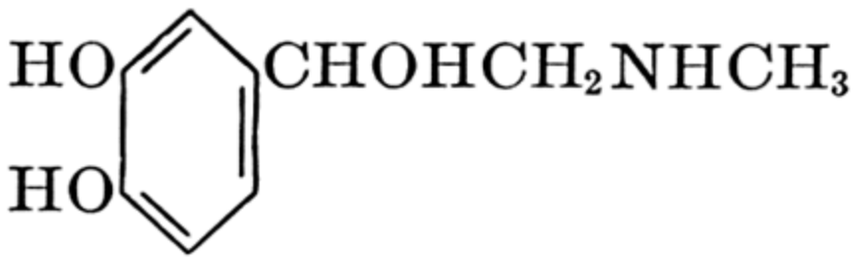
cholinergic. In this group are both types of autonomic nerves as well as the somatic motor nerves to skeletal muscles.

The adrenal medulla which secretes epinephrine is innervated by preganglionic sympathetic nerve fibers and is therefore stimulated by acetylcholine. Thus, the apparent anomaly of the stimulation of the secretion of the medullary hormone by its physiological antagonist has found a rational explanation. The recognition of acetylcholine as the chemical which sets in motion the reactions leading to muscular contraction is further support for the correctness of the classification of nerves on a chemical basis.[4]

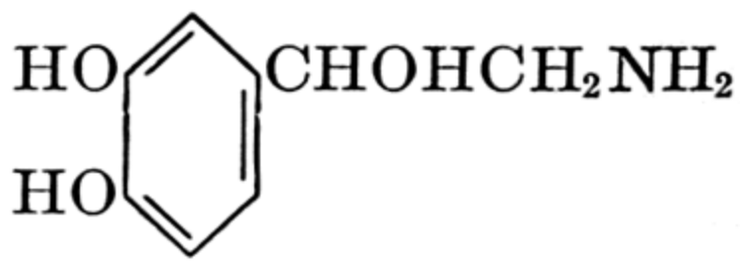
3. Epinephrine and Norepinephrine

The impulses of postganglionic sympathetic nerves release substances which produce in the innervated organ effects very similar to those of epinephrine, the hormone of the adrenal medulla. Cannon called the substances sympathin and regarded them as identical with epinephrine (3,4-$(HO)_2C_6H_3CHOHCH_2NHCH_3$). Dale, using the brand name Adrenalin instead of the then not yet coined name epinephrine, introduced the designation of *adrenergic* nerves for sympathetic postganglionic nerve fibers capable of releasing sympathin.

The true nature of sympathin has only recently been established with some certainty. It consists of two chemical compounds, epinephrine, (Adrenalin XIX-1) and L-norepinephrine (L-Arterenol, XIX-2). The



(XIX-1)



(XIX-2)

two compounds have been separated[5] from the natural hormone mixture from adrenal glands (perhaps from nerves) by filter paper chromatography and by other fractionation methods. They appear to occur in the mixture at an approximately constant ratio, regardless of the animal source. This finding explains many previous incongruous observations of apparently contradictory pharmacodynamic activities of natural sympathin, such as differences in cardiac and intestinal and also in pressor actions. For a long time, the existence of two sympathins (E and I) had been suspected, and even their true chemical structure had been intimated. The separa-

[4] Dale, *Science*, **90,** 393 (1939).

[5] Goldenberg, Faber, Alston, and Chargaff, *Science*, **109,** 534 (1949). Tullar, *ibid.*, 536. Auerbach and Angell, *ibid.*, 537. Euler, *Arch. Intern. Pharm. Therap.*, **77,** 477 (1948); Mann and West, *Brit. J. Pharmacol. Chemother.*, **5,** 173 (1950).

TABLE I.[7] PRINCIPAL EFFECTS OF STIMULATION OF AUTONOMIC NERVES

Tissue	Effects of stimulation of Nerves	
	Sympathetic	Parasympathetic
Eye:—Pupil	Dilated	
Tension (too high in glaucoma)	Increased	-
Eyeball	Protruded (toxic goitre)	Withdrawn
Tears	Unchanged	Increased
Digestive glands		
Secretion	Slightly increased	Greatly increased
Blood flow	Decreased	Increased
Respiratory tract		
Muscle	Relaxed	Contracted (asthma)
Secretion	?	Increased
Circulation	Decreased	Increased
Heart		
Rate	Increased	Decreased
Force	Increased	Decreased (auricles)
Blood vessels		
Skin	Strongly constricted	Dilated*
Abdominal organs	Strongly constricted	Dilated*
Muscles	Weakly constricted	Dilated*
Brain	Very weakly constricted	Dilated*
Lungs	Very weakly constricted	Dilated*
Coronaries	Dilated	Dilated*
Involuntary muscle		
Stomach and intestines	Relaxed	Contracted
Urogenital tract	Variable	Contracted
Sweat Secretion	?	Increased*

*Innervation anatomically sympathetic but physiologically and pharmacologically parasympathetic

tion of the two compounds will now lead to clarifications of previously confusing pharmacological findings. Some pharmacologists still prefer to think of two types of cell chemicals, the α- and β-receptors, which are supposed to account for divergent pressor effects.

In view of these recent discoveries, the whole field of autonomic drugs is now in flux and older attempts to explain incongruencies are rapidly being reviewed. Even the most authoritative and newest monograph[6] on this subject has not yet covered these developments. Renewed active interest

[6] Bovet and Bovet-Nitti, *Structure et Activité Pharmacodynamique des Médicaments du Système Nerveux Végétatif.* Interscience, New York, 1948.

[7] Adapted from lecture notes by Schmitt, "Pharmacology for Chemists," Philadelphia, 1948.

in the theories and uses of autonomic drugs in innumerable laboratories and clinics has contributed to this situation.

There is every indication that norepinephrine is the immediate precursor of epinephrine, and that the latter is formed from the nor-compound by transmethylation under the influence of adenosine triphosphate. Typical arguments for this mechanism rest on physiological evidence.[8]

4. Physiological Action of Autonomic Drugs

An autonomic drug, in promoting or blocking nervous transmission, may be pictured as interfering with the following series of events. A nerve is stimulated preganglionically; this leads to an impulse which causes liberation of acetylcholine at the ganglionic synapse. The post-ganglionic impulse received through the mediation of this chemical makes the nerve end-organ liberate acetylcholine, or epinephrine or norepinephrine at the junction with gland or muscle cells (myoneural junction), depending on the type of nerve fiber. The liberated chemical mediator now combines with chemicals of the "receptor cell", probably enzymes of muscle or gland cells, and this chemical reaction leads to the specific response of the stimulated organ which is observed by the pharmacologist.

In view of the classification of autonomic nerves as cholinergic and adrenergic, drugs eliciting effects similar to the stimulation of these nerves are now often spoken of as cholinergic, and adrenergic stimulants and blocking agents.

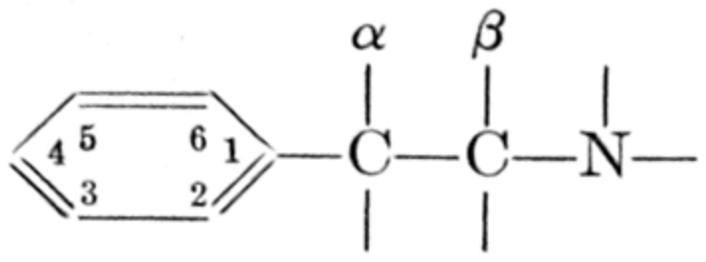
II. THE SYMPATHOMIMETIC AMINES

1. The Work of Barger and Dale

It had been known since the early observations of Vulpius (1856) that a secretion (now called a hormone) of the adrenal medulla can raise the blood pressure in laboratory animals and in man. After the isolation, purification, and the elucidation of the structure of its main component shortly after 1900, the similarity of its chemical properties and those of certain putrefactive amines attracted the attention of Barger and Dale.[9] In a now famous and comprehensive investigation, they synthesized a series of compounds having in common the phenethylamine grouping (XIX-3), and with substituents at the α- or β-carbon atoms as well as in the benzene ring. These amines were tested as vasopressors. Since many of them simulated effects of epinephrine, that is, mimicked the effect of stimulating

[8] Beyer, *Abstracts*, Meeting Am. Soc. Pharmacol. Exper. Therap., Indianapolis, Nov. 17, 1949, p. 11.

[9] Barger and Dale, *J. Physiol.*, **41,** 19 (1910).



(XIX-3)

the sympathetic nervous system, Barger and Dale coined for their compounds the term sympathomimetic amines. If they raise the blood pressure, they are called vasopressors. Compounds which lower the blood pressure are spoken of as vasodepressors.

As pointed out above, epinephrine and most likely norepinephrine have also been identified as the chemical mediators of postganglionic sympathetic nervous impulses. The sympathomimetics have been defined as products whose physiological action is peripheral in nature, and which produce, similar to the sympathetic mediators, a rise in blood pressure coupled with capillary vasoconstriction. They also diminish the tone of certain smooth muscles, such as the uterus or the intestines.

This definition does not take into account other phenomena observed with certain members of this group. At least one type of activity should be included, namely the centrally excitatory action of several important sympathomimetics. The analeptic amines centered around Benzedrine must therefore be mentioned as a special sub-group.

The conclusions drawn from the early studies will be reviewed later in a discussion of the relation of the chemical structure and the pharmacodynamic properties of this class of compounds. They heralded the development of the field as we know it today, but for almost fifteen years epinephrine (Adrenalin) remained the only therapeutically useful member of the group. The discovery of the advantageous adrenergic properties of ephedrine by Chen[10] in 1923, and the subsequent rapid addition of valuable therapeutic agents to this series (amphetamine, Neosynephrine, Isuprel, etc.) were a direct outcome of the pioneer experiments of the earlier British authors.

2. Formation from Proteins

The naturally occurring adrenergic amines, including epinephrine and norepinephrine, are regarded as degradation products of proteinogenous amino acids of the diet and the tissues. The amino acids (XIX-4) of the cell proteins are ordinarily deaminated by dehydrogenases to imino acids (XIX-5) which are then hydrolyzed to ammonia and carbonyl derivatives (XIX-6). The latter may undergo a variety of further biochemical transmutations.

[10] Chen and Schmidt, *J. Pharmacol. Exptl. Therap.*, **24,** 339 (1924).

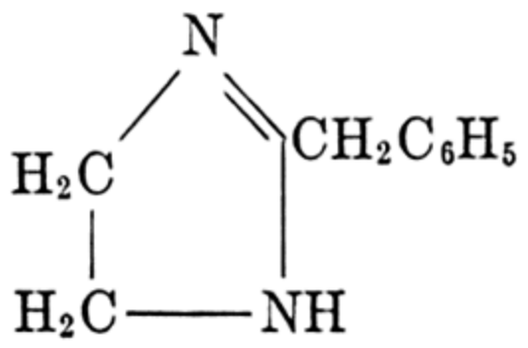
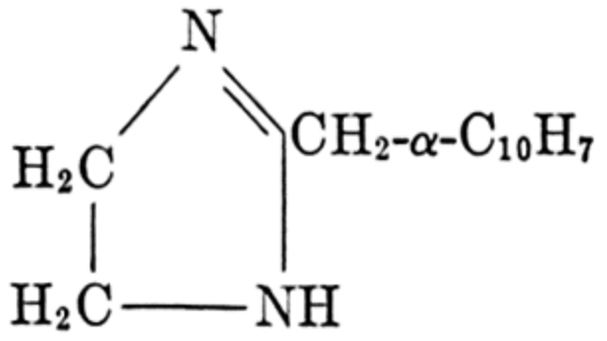
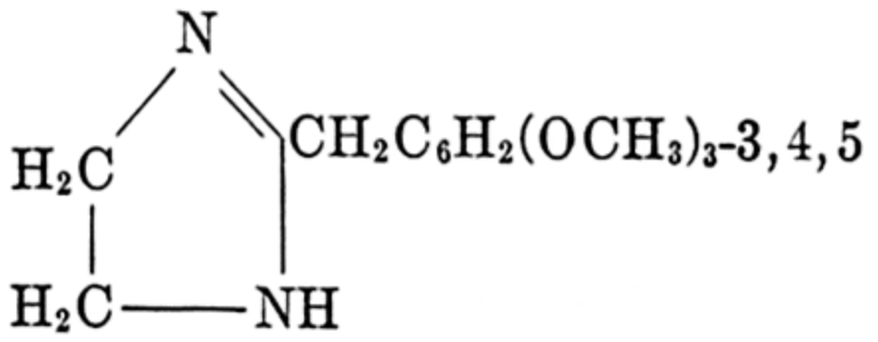
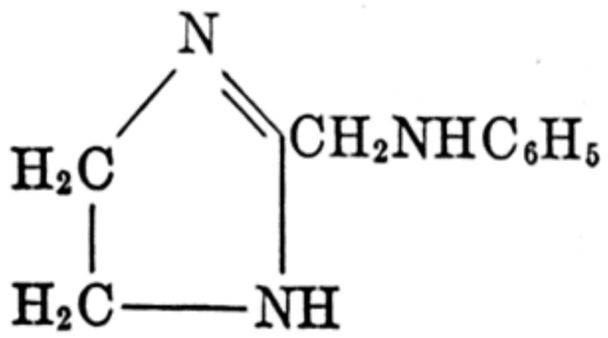
TABLE II. SOME USEFUL PRESSOR AMINES

Common Names	Chemical Name	Structure	Principal Uses
Benzedrine Amphetamine *d*-Form: Dexedrine	1-Phenyl-2-aminopropane	$C_6H_5CH_2CH(CH_3)NH_2$	Vasopressor, Analeptic, Anorexic, Nasal Shrinker
Vonedrine	1-Methylamino-2-phenyl-propane	$C_6H_5CH(CH_3)CH_2NHCH_3$	Non-stimulating Vaso-constrictor
Pervitin *d*-Form: Methedrine	1-Phenyl-2-methylamino-propane	$C_6H_5CH_2CH(CH_3)NHCH_3$	Central Stimulant, Vaso-pressor
Tyramine, Uteramine, Systogene	4-Hydroxyphenethylamine	$4\text{-}HOC_6H_4CH_2CH_2NH_2$	Vasopressor
Hordenine, Anhaline	N,N-Dimethyl-4-hydroxy-phenethylamine	$4\text{-}HOC_6H_4CH_2CH_2N(CH_3)_2$	Antiperistaltic, Anti-diarrhetic
Epinine	3,4-Dihydroxy-N-methyl-phenethylamine	$3,4\text{-}(HO)_2C_6H_3CH_2CH_2NHCH_3$	Uterine Contractor
Paredrine	1-(4-Hydroxyphenyl)-2-aminopropane	$4\text{-}HOC_6H_4CH_2CH(CH_3)NH_2$	Mydriatic; Non-stimu-lating Vasopressor
Veritol, Paredrinol	1-(4-Hydroxyphenyl)-2-methylaminopropane	$4\text{-}HOC_6H_4CH_2CH(CH_3)NHCH_3$	Venous Constriction
Orthoxine	1-(2-Methoxyphenyl)-2-methylaminopropane	$2\text{-}CH_3OC_6H_4CH_2CH(CH_3)NHCH_3$	Bronchodilator
Mescaline	3,4,5-Trimethoxyphen-ethylamine	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH_2NH_2$	Euphoriant
Mephentermine	1-Phenyl-2-methyl-2-methylaminopropane	$C_6H_5CH_2C(CH_3)_2NHCH_3$	Nasal Shrinker
Neosynephrine	*l*-1-(3-Hydroxyphenyl)-2-methylaminoethanol	$3\text{-}HOC_6H_4CHOHCH_2NHCH_3$	Nasal Shrinker, Vaso-constrictor
Sympatol, Synephrine	1-(4-Hydroxyphenyl)-2-methylaminoethanol	$4\text{-}HOC_6H_4CHOHCH_2NHCH_3$	Vasopressor

Common Names	Chemical Name	Structure	Principal Uses
Suprifine	1-(4-Hydroxyphenyl)-2-methylaminopropanol	$4\text{-}HOC_6H_4CHOHCH(CH_3)NHCH_3$	Vasopressor
Propadrine	1-Phenyl-2-aminopropanol	$C_6H_5CHOHCH(CH_3)NH_2$	Vasopressor, Nasal Shrinker
Ephedrine	1-Phenyl-2-methylaminopropanol	$C_6H_5CHOHCH(CH_3)NHCH_3$	Vasopressor, Analeptic, Antiasthmatic
Nethacol	*l*-1-Phenyl-2-ethylaminopropanol	$C_6H_5CHOHCH(CH_3)NHC_2H_5$	Bronchodilator
Methadren	1-(3,4-Dihydroxyphenyl)-2-dimethylaminoethanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH_2N(CH_3)_2$	Hyperglycemic
Norepinephrine, (rac): Arterenol	1-(3,4-Dihydroxyphenyl)-2-aminoethanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH_2NH_2$	Vasoconstrictor
Epinephrine, Adrenaline, Suprarenalin	*l*-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH_2NHCH_3$	Vasoconstrictor, Bronchodilator
Cobefrine	1-(3,4-Dihydroxyphenyl)-2-aminopropanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH(CH_3)NH_2$	Orally Active Vasoconstrictor, Analeptic
Isuprel, Aludrine	1-(3,4-Dihydroxyphenyl)-2-isopropylaminoethanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH_2NHCH(CH_3)_2$	Orally Active Bronchodilator
Butanefrine	1-(3,4-Dihydroxyphenyl)-2-aminobutanol	$3,4\text{-}(HO)_2C_6H_3CHOHCH(C_2H_5)NH_2$	Bronchodilator
Adrenalone, Kephrine, Styphnone	4-Methylaminoacetyl catechol	$3,4\text{-}(HO)_2C_6H_3COCH_2NHCH_3$	Vasoconstrictor

Table continued

TABLE II. SOME USEFUL PRESSOR AMINES (*Continued*)

Common Names	Chemical Name	Structure	Principal Uses
Priscolin	2-Benzylimidazoline		Vasodilator
Privine	2-α-Naphthylmethylimidazoline		Vasoconstrictor
Phedrazine	2-(3,4,5-Trimethoxybenzyl)imidazoline		Vasoconstrictor
Otrivine	2-Anilinomethylimidazoline		Long-lasting Vasopressor
Oenethyl	2-Methylaminoheptane	$CH_3NHCH(CH_3)(CH_2)_4CH_3$	Volatile Vasopressor
Tuamine	2-Aminoheptane	$H_2NCH(CH_3)(CH_2)_4CH_3$	Volatile Vasopressor
Octin	2-Methylamino-6-methylheptene-5	$CH_3C(CH_3)=CH(CH_2)_2CH(CH_3)NHCH_3$	Volatile Vasopressor
Cyverine	1-Dicyclohexyl-2-methylaminoethane	$(cyclo\text{-}C_6H_{11})_2CHCH_2NHCH_3$	Vasoconstrictor
Benzedrex	1-Cyclohexyl-2-methylaminopropanol	$cyclo\text{-}C_6H_{11}CH_2CH(CH_3)NHCH_3$	Nasal Shrinker

$$\underset{\text{(XIX-4)}}{RCH(NH_2)CO_2H} \xrightarrow{-2H} \underset{\text{(XIX-5)}}{RC(=NH)CO_2H} \xrightarrow{HOH} RCOCO_2H + NH_3 \quad \underset{\text{(XIX-6)}}{}$$

However, especially under putrefactive conditions, decarboxylation under the influence of carboxylase takes place rather than dehydrogenation. If any of the β-substituted aromatic or heterocyclic derivatives of alanine

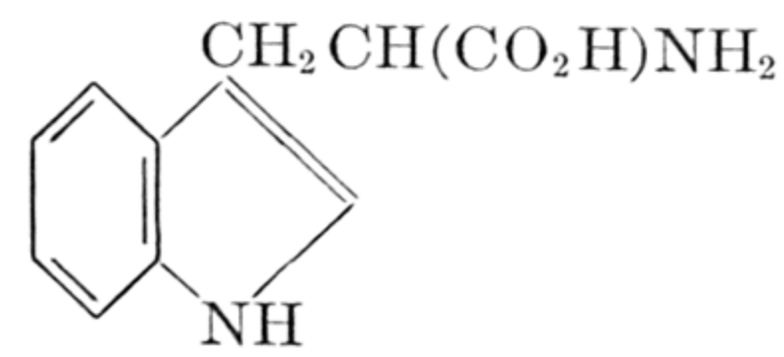
$$RCH(NH_2)COOH \rightarrow RCH_2NH_2 + CO_2$$

become subject to decarboxylation, the corresponding β-ethylamines may be formed. Phenylalanine (XIX-7) is converted to phenethylamine (XIX-8), tyrosine (XIX-9) to tyramine (XIX-10), "dopa" (XIX-11) to 3,4-dihydroxyphenethylamine (XIX-12), tryptophan (XIX-13) to tryptamine (XIX-14), and histidine (XIX-15) to histamine (XIX-16).

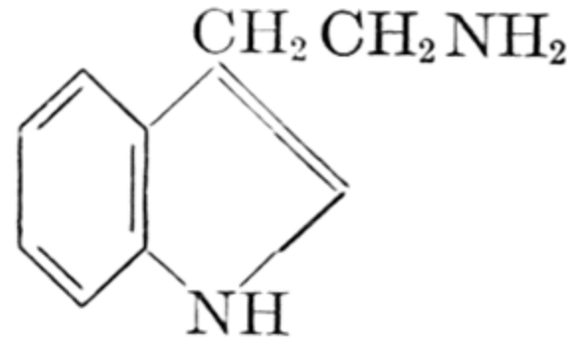
$$\underset{\text{(XIX-7)}}{C_6H_5CH_2CH(COOH)NH_2} \rightarrow \underset{\text{(XIX-8)}}{C_6H_5CH_2CH_2NH_2}$$

$$\underset{\text{(XIX-9)}}{p\text{-}HOC_6H_4CH_2CH(COOH)NH_2} \rightarrow \underset{\text{(XIX-10)}}{p\text{-}HOC_6H_4CH_2CH_2NH_2}$$

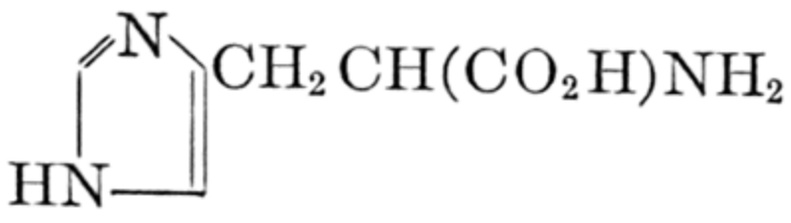
$$\underset{\text{(XIX-11)}}{3,4\text{-}(HO)_2C_6H_3CH_2CH(COOH)NH_2} \rightarrow \underset{\text{(XIX-12)}}{3,4\text{-}(HO)_2C_6H_3CH_2CH_2NH_2}$$



(XIX-13)



(XIX-14)



(XIX-15)



(XIX-16)

Phenethylamine, tyramine, 3,4-dihydroxyphenethylamine and histamine have been found in putrefaction products of proteins. The first three of these biogenic amines raise the blood pressure by vasoconstriction, while histamine has the opposite effect (vasodilation.)

The alanine side chain of some of the amino acids mentioned can be decarboxylated as well as oxidized in successive steps. The well known reactivity of the benzyl carbon atom ($ArCH_2CH(COOH)NH_2$), and the common occurrence of aromatic acids (ArCOOH) among the end-products

of biological oxidations support the view that oxidation at the benzyl position may be expected without difficulty. The presence of epinephrine ($3,4\text{-}(HO)_2C_6H_3CHOHCH_2NHCH_3$) in mammals, and in other animal tissues, is further proof of this oxidative mechanism. An epinephrine-like substance has also been synthesized from phenethylamine, phenylalanine and tyramine *in vitro*.[11]

Tyramine, and its oxidation product (XIX-12, 3,4-dihydroxyphenethylamine) are undoubtedly biological precursors of epinephrine and norepinephrine. In the rat, phenylalanine labeled with C^{14} both in the carboxyl group and at the alpha-carbon atom (XIX-17), is converted to epinephrine in which the C^{14} is localized at the terminal carbon atom of the side chain (XIX-18).[12]

$$C_6H_5CH_2C^{14}HC^{14}O_2H \rightarrow (HO)_2C_6H_3CHOHC^{14}H_2NHCH_3$$

$$\begin{array}{c} | \\ NH_2 \end{array}$$

(XIX-17) (XIX-18)

All the natural phenethylamines are toxic. In order to detoxicate the small natural amounts rapidly and safely, the body has at its command enzymes which are specifically concerned with this task. The purely synthetic members of the phenethylamine series act apparently by interfering with the normal chemical reactivity of these enzymes, thereby prolonging the "toxic" effect of the natural substrates of the biocatalysts. If this "toxic" effect is therapeutically valuable, the synthetic compound will be a welcome addition to the growing series of functional autonomic drugs.

Not all effects of synthetic autonomic drugs can be explained in this manner. Some aspects of this problem will be discussed under the heading of enzymatic inactivation of phenethylamines. A description of epinephrine and of the more interesting adrenergic amines, their chemical properties, syntheses, and specific therapeutic value will precede a general pharmacological evaluation, and attempts to correlate their activity and chemical structure.

That the aromatic ring is not absolutely essential for pressor activity is attested by the weak pressor action of isoamylamine which is found naturally as a putrefaction product of leucine. Other aliphatic amines share in this property, and some, for instance 2-aminoheptane, have found therapeutic use. Nevertheless, the arylethylamines possess a much higher order of activity.

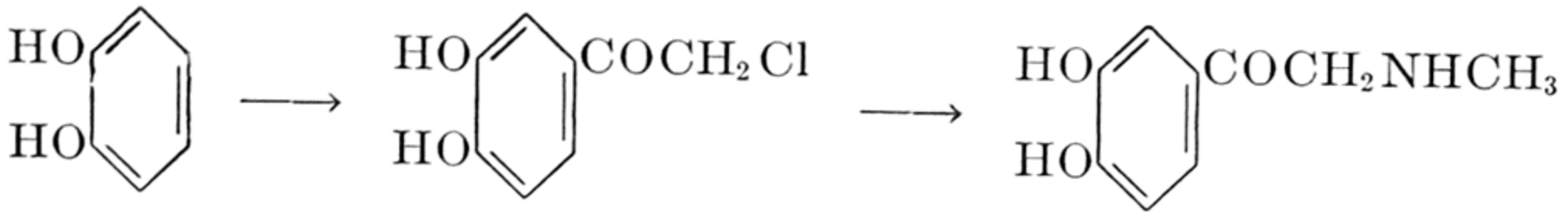
[11] Devine, *Biochem. J.*, **34,** 2 (1940).
[12] Gurin and Delluva, *J. Biol. Chem.*, **170,** 545 (1947).

3. Epinephrine

Epinephrine, one of the hormones of the mammalian adrenal medulla, is the levorotatory form of a base which has been given the brand names Adrenalin or Suprarenalin. It was isolated in the pure state around the turn of the century by various groups of workers headed by Abel, von Fürth and Takamine. A review of these historic events has been presented by Hartung.[13]

Although synthetic Adrenalin became available soon after the structure of the hormone had been elucidated, the synthetic DL-base has not been used widely in medicine because the natural levorotatory form is about 15 times as active as the racemic mixture. To be sure, the optical resolution with tartaric acid offers no insuperable difficulties,[14] and the mother liquors of the (−) form, containing largely the only weakly active (+) Adrenalin, can be racemized with hot hydrochloric acid and thus recycled into the resolution process.[15] Nevertheless, at least in the United States, (−) epinephrine can be extracted from the adrenal glands of cattle more economically than it could be synthesized. The glands, a by-product from the stock yards, are extracted with dilute mineral acid, and (−) Adrenalin hydrochloride is obtained by concentration and adsorption of contaminants without isolation of the air-sensitive free base.

The only commercial synthesis of Adrenalin which has been used especially in Europe, is an adaptation of the original method of Stolz.[16] Catechol is converted to 4-chloroacetyl catechol (XIX-19) by means of acetyl chloride, in the presence of traces of zinc chloride, or by chloroacetic acid and phosphorus oxychloride. The chloroketone is treated with methylamine, and the methylamino ketone (XIX-20, adrenalone, stryphnone, kephrine) is reduced by chemical, catalytic or electrolytic methods.[17]



(XIX-19) (XIX-20)

(XIX-1)

[13] Hartung, *Chem. Revs.*, **9,** 389 (1931).
[14] Flächer, *Z. physiol. Chem.*, **58,** 189 (1908).
[15] Höchster Farbwerke, German Pat. 220,355 (1910).
[16] Stolz, *Ber.*, **37,** 4149 (1904).
[17] Waser, *Synthese der organischen Arzneimittel.* Enke, Stuttgart, 1928.

In order to avoid the resolution of DL-Adrenalin, adrenalone (XIX-20) has also been hydrogenated in the presence of D-tartaric acid.[18] The D-bitartrate of the (−) base crystallizes directly from the methanolic reaction mixture while the salt of the (+) base remains in solution.

Adrenalone has been used in its own right as a more sustained sympathomimetic amine of moderate activity. The intermediate chloroketone (XIX-19) is a commercial intermediate in the production of Arterenol and Isuprel.

The pronounced vasoconstrictive action of epinephrine has led to the extensive use of the drug as a topical hemostat. It also relieves readily congestion of the nasal mucosa by constricting the blood vessels of this membrane but has been replaced largely for this purpose by other sympathomimetic amines with fewer side-effects, or greater volatility.

The vasoconstrictor action of epinephrine has made it an important component in mixtures with synthetic local anesthetics which lack this property themselves. Under the influence of the vasoconstrictor the anesthetic is absorbed less rapidly; this means longer duration of the anesthesia and smaller doses of the anesthetic, and therefore, less danger of toxic effects in the system.

Epinephrine accelerates the heart and has found therapeutic application in cardiac diseases. Even cardiac failure and arrest can be overcome occasionally by direct injection of the drug into the heart but the success of this mode of resuscitation is not always certain. As in all other applications, epinephrine must be used with utmost caution if hypertension, angina pectoris or coronary thrombosis are involved.

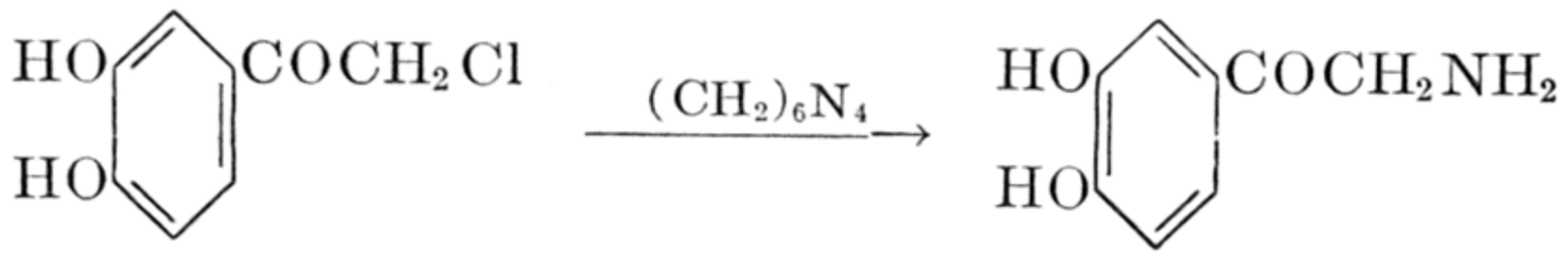
The main and, until recently, almost unrivalled clinical use of epinephrine has been in the control of severe allergic symptoms, especially bronchial asthma. Because it is inactive when taken orally, epinephrine is usually injected subcutaneously, less frequently intravenously, and affords rapid relief from the distressing asthmatic symptoms. In order to prolong its action, the drug may sometimes be given intramuscularly in a suspension in peanut oil. It diffuses slowly from the muscles into the circulation. It is also available in glycerol for inhalation from a vaporizer; in this way, it comes most rapidly in contact with constricted, spastic bronchies.

In doses much larger than needed to produce a rise in blood pressure, epinephrine exhibits glycogenolytic activity, that is, it raises the amount of glucose in the blood by promoting depolymerization of the storage carbohydrate, glycogen, in the liver or muscles. It thereby counteracts the pancreatic hormone insulin which reduces the concentration of blood sugar by various mechanisms. There seems to be no causal connection between the glycogenolytic and pressor effects of Adrenalin.

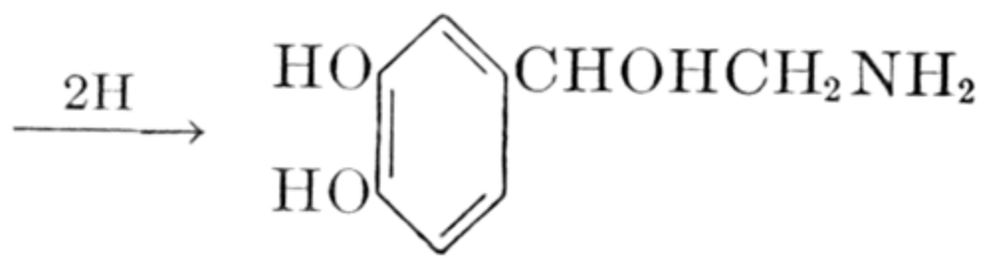
[18] Ishiwara, *Ber.*, **57,** 1125 (1924).

4. Amine Homologs of Epinephrine

By condensing 4-chloroacetylcatechol (XIX-19) with hexamethylene tetramine, a primary amino ketone (XIX-21) is obtained which can be reduced to DL-norepinephrine, (Arterenol, XIX-2), the racemic form of the natural hormone.

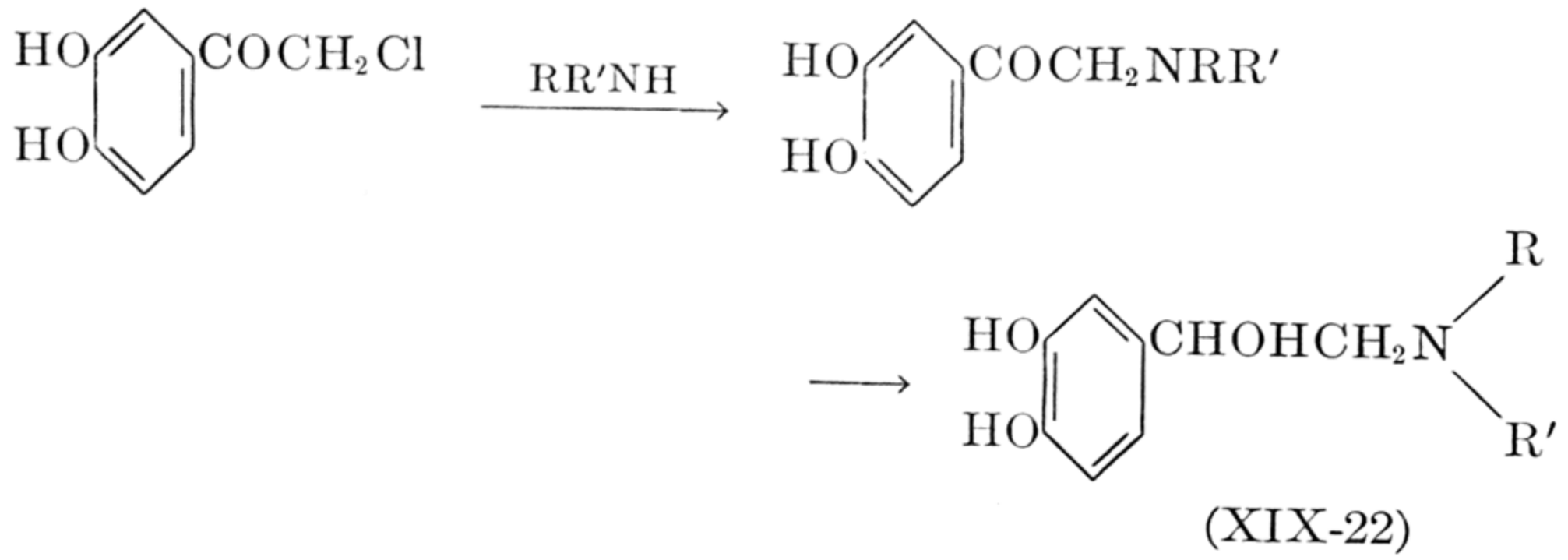


(XIX-19) (XIX-21)



(XIX-2)

If primary or secondary amines are used as reagents, a series of homologs of Adrenalin can be evolved (XIX-22). Of these, DL-1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol (aludrine, Isuprel) has been shown to be the least toxic and most powerful bronchodilator in this series (Chapter



(XIX-22)

XIX, III-2). Its important advantage lies in its action on blood pressure: it is a vasodilator, lowers the blood pressure and mitigates the anxiety syndrome accompanying asthmatic attacks.

The tertiary amine Methadren (N-methyladrenaline, 3,4-$(HO)_2C_6H_3$-$CHOHCH_2N(CH_3)_2$) is only $\frac{1}{600}$th as active a pressor as L-epinephrine, but its action on blood sugar is almost the same as that of the hormone.[19]

[19] Stutzman and Orth, *J. Pharmacol. Exptl. Therap.*, **69,** 1 (1940).

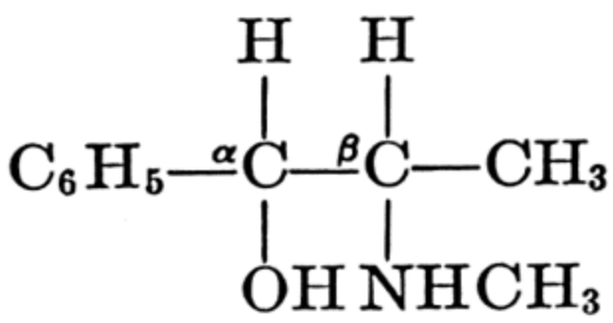
5. Ephedrine

Ephedrine, 1-phenyl-2-methylaminopropanol (XIX-23), is an alkaloid from the stems of a gymnosperm of the genus *Ephedra* which is found in the temperate zones of Eurasia and America. Under the name of Ma Huang an ephedrine containing species had been known to the Chinese for over 5,000 years. It is recorded that the ancient emperor Shen Nung (2760 B.C.) introduced the drug Ma Huang into the medical practice of his country, recommending it as a medicine for cough, fever, and heart trouble, and probably as a stimulant to press more work out of slave laborers.

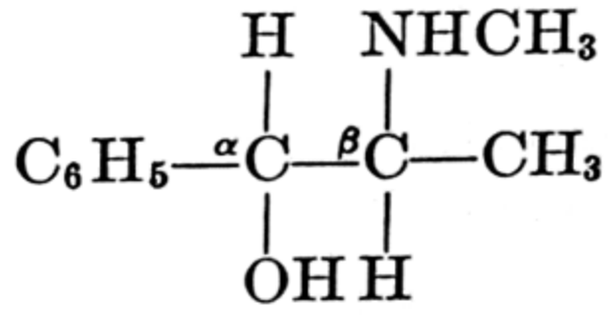
The alkaloid, a levorotatory base, was isolated in the pure state from *Ephedra vulgaris* by Nagai[20] and named by him ephedrine. It was first synthesized by Späth and Göhring[21] by a complex route which confirmed its structure.

The important pharmacodynamic properties of ephedrine were discovered accidentally by Chen[22] who observed that ephedrine produced a rise in blood pressure similar to that obtainable with epinephrine. The similarity of the chemical formulas of ephedrine and epinephrine was recognized as a possible cause of the similar pharmacodynamic behavior of the two substances, and this idea provided the incentive for the rapid development of the large number of other sympathomimetic derivatives of phenethylamine which had been stagnant since the suggestive study of Barger and Dale.[9]

Ephedrine contains two unlike asymmetric carbon atoms, and diastereoisomeric forms are therefore to be expected. The two possible racemic mixtures are called ephedrine (XIX-23), and pseudoephedrine (XIX-24), respectively. Evidence for the configurations assigned to these forms may be found in papers by Leithe and by Freudenberg.[23] Only D(−)



(XIX-23)



(XIX-24)

[20] Nagai, *Pharm. Ztg.*, **32,** 700 (1887).

[21] Späth and Göhring, *Monatsh.*, **41,** 319 (1920).

[22] Chen and Schmidt, *J. Pharmacol. Exptl. Therap.*, **24,** 339 (1924); *Medicine*, **9,** 7 (1930). Chen and Schmidt, *Ephedrine and Related Substances*, Williams & Wilkins, Baltimore, 1930.

[23] Leithe, *Ber.*, **65,** 660 (1933). Freudenberg and Nikolai, *Ann.*, **510,** 223 (1934). Compare also Fodor, Bruckner, Kiss, and Ohegyi, *J. Org. Chem.*, **14,** 337 (1949).

ephedrine and L(+)ψ-ephedrine are found in nature. The α-carbon atom of both these forms has been shown to be dextrorotatory; it seems that this property provides greater pharmacological activity than the opposite configuration.[24] The two naturally occurring forms of ephedrine are more mydriatic than their optical isomers, D(+)ephedrine and L(−)ψ-ephedrine, respectively. On the other hand, the differences of the pharmacodynamic properties of DL-ephedrine and its component, D(−)ephedrine, are not striking enough to justify the laborious optical resolution of the synthetic racemic mixture. The latter is marketed as the hydrochloride or sulfate, and used to be called ephetonine or racephedrine.

One of the commercial syntheses[25] of ephedrine builds up the side chain by condensing benzaldehyde with nitroethane, and reducing the nitro alcohol (XIX-25) to a mixture of diastereoisomeric 1-phenyl-2-amino-propanols (XIX-26 and 27) which can be separated by fractional crystallization. Methylation of the amino group yields ephedrine (XIX-23) and ψ-ephedrine (XIX-24), respectively.

$$C_6H_5CHO + \begin{matrix} CH_2NO_2 \\ | \\ CH_3 \end{matrix} \longrightarrow \underset{\text{(XIX-25)}}{C_6H_5CHOHCH(CH_3)NO_2}$$

$$\xrightarrow{H_2} \begin{cases} \underset{\text{(XIX-26)}}{C_6H_5\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{NH_2}{C}}CH_3} \longrightarrow \underset{\text{(XIX-23)}}{C_6H_5\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{CH_3NH}{C}}-CH_3} \\ \underset{\text{(XIX-27)}}{C_6H_5\overset{H}{\underset{OH}{C}}-\overset{NH_2}{\underset{H}{C}}CH_3} \longrightarrow \underset{\text{(XIX-24)}}{C_6H_5\overset{H}{\underset{OH}{C}}-\overset{CH_3NH}{\underset{H}{C}}-CH_3} \end{cases}$$

The ψ-ephedrine need not be wasted. It can be rearranged to ephedrine to a large extent by heating with 25% hydrochloric acid. It can also be oxidized to the corresponding methylamino ketone (XIX-27) which is reduced again to a diastereoisomeric mixture from which additional quantities of ephedrine can be recovered.

$$\underset{\text{(XIX-24)}}{C_6H_5\overset{H}{\underset{OH}{C}}-\overset{NHCH_3}{\underset{H}{C}}CH_3} \xrightarrow{(O)} \underset{\text{(XIX-27)}}{C_6H_5COCH(CH_3)NHCH_3} \xrightarrow{H_2} \begin{cases} \text{(XIX-23)} \\ \text{(XIX-24)} \end{cases}$$

[24] Jarowski and Hartung, *J. Org. Chem.*, **8,** 564 (1943).
[25] Fourneau and Kanao, *Bull. soc. chim.* (4) **35,** 614 (1924). Kanao, *J. Pharm. Soc. Japan*, **1927,** 17.

In another reaction which furnishes only D(−)ephedrine, glucose is fermented by the enzyme carboligase from yeast in the presence of benzaldehyde.[26] The latter is transformed to (−)-1-phenyl-2-ketopropanol (XIX-28) which is hydrogenated in a mixture with methylamine. The product is identical with natural (−) ephedrine.

$$C_6H_5CHO + C_6H_{12}O_6 \xrightarrow{\text{Carboligase}} C_6H_5CHOHCOCH_3$$
(XIX-28)

$$\xrightarrow[NH_2CH_3]{H_2,\ Pt\ or\ Al} \text{(XIX-23)}$$

Ephedrine is a weak vasopressor amine in comparison with epinephrine; it has only 0.005 to 0.01 the effect of the latter. However, perhaps because of the absence of the labilizing catechol structure, ephedrine is much more stable; its action lasts 7 to 10 times as long as that of epinephrine, and in addition, it can be administered by mouth. Its toxicity is about $\frac{1}{400}$th that of the hormone. The prolonged action of ephedrine makes it useful in maintaining a satisfactory blood pressure during spinal anesthesia. In heart disease or hypotensive conditions requiring repeated medication with a vasopressor, the oral route of using ephedrine offers a definite advantage.

Apart from its sustained vasoconstrictor effects which serve a useful purpose in the control or prophylaxis of mild or chronic bronchial asthma, ephedrine also stimulates the respiratory centers, a property which epinephrine does not possess. This centrally excitant activity also counteracts the depression caused by morphine or barbiturates, and wakens narcoleptic patients to normal levels of activity.

Ephedrine has been the drug of choice of many individuals in the symptomatic relief from attacks of hay fever. It also relieves congested mucosal conditions in the nose and the upper respiratory tract. Here again its long-lasting effect is much appreciated. The free crystalline base may be vaporized in an oil emulsion for these applications.

Ephedrine produces mydriasis of brief duration, which is quite valuable for short ophthalmological observation. It is also a valuable adjunct to the control of myasthenia gravis (Chapter XXI) by Prostigmine. The biochemical mechanism of this activity is not understood.[27]

[26] Bockmühl, Stein, and Ehrhart, U. S. Pat. 1,962,476 (1934). Hildebrandt and Klavehn, U. S. Pat. 1,956,950 (1934).

[27] Schlezinger, *Arch. Int. Med.*, **65,** 60 (1940).

6. Homologs and Analogs of Ephedrine

a. Nethacol

Nethacol is *l*-1-phenyl-2-ethylaminopropanol, $C_6H_5CHOHCH(CH_3)$-NHC_2H_5. It can be administered orally to asthma patients and dilates the bronchies for almost as long a period as ephedrine. It compares in toxicity with the parent alkaloid but has only about 0.1 its pressor action.[28]

b. Neosynephrine

Neosynephrin, *l*-1-(3-hydroxyphenyl)-2-methylaminoethanol, *m*-HOC_6-$H_4CHOHCH_2NHCH_3$, has barely any excitant effect on the central nervous system and is used in place of ephedrine wherever this activity is undesirable. It is a favorite active ingredient of nasal membrane shrinkers but is suitable as well for other vasoconstrictor purposes. It has superseded the less active racemic *p*-isomer, *p*-$HOC_6H_4CHOHCH_2NHCH_3$, (Synephrine, Sympathol); the pressor activity of Neosynephrine is one fifth that of epinephrine; its action lasts twice as long.[29] Norsympathol (*p*-$HOC_6H_4CHOHCH_2NH_2$) also stimulates the circulation.

c. Propadrine

Propadrine, (DL-norephedrine, 1-phenyl-2-aminopropanol), C_6H_5CHOH-$CH(CH_3)NH_2$, has a slightly higher vasopressor, and a lower toxic and centrally stimulatory activity than ephedrine. It is incorporated in a jelly as a nasal shrinker, and may be used in place of ephedrine for most purposes.[30] It is chemically stable and active when administered by mouth. The levorotatory form has been found as a minor alkaloid in *Ephedra* species.

The synthesis of Propadrine starts with propiophenone which is nitrosated with butyl nitrite and hydrogen chloride. The isonitroso derivative (XIX-29) is hydrogenated to DL-Propadrine (XIX-30).[31]

$$C_6H_5COCH_2CH_3 \xrightarrow{HONO} C_6H_5COC(CH_3)=NOH \xrightarrow[cat.]{H_2} C_6H_5CHOHCH(CH_3)NH_2$$

(XIX-29) (XIX-30)

[28] Becker, Warren, Marsh, Thompson, and Shelton, *J. Pharmacol. Exptl. Therap.*, **75,** 289 (1942).

[29] Tainter and Seidenfeld, *J. Pharmacol. Exptl. Therap.*, **40,** 23 (1930). Ehrisman, *Deut. med. Wochschr.*, **53,** 1263 (1927).

[30] Chen, Wu, and Henriksen, *J. Pharmacol. Exptl. Therap.*, **36,** 363 (1929).

[31] Hartung and Munch, *J. Am. Chem. Soc.*, **51,** 2262 (1929).

d. Suprifine

p-Hydroxyephedrine (*p*-$HOC_6H_4CHOHCH(CH_3)NHCH_3$) has been used under the name of Suprifine. It has typical adrenergic properties. The *meta* isomer acts as an analeptic.[32] On the other hand, the primary amine in the *m*-hydroxy series (XIX-31) has a prolonged vasopressor but barely any central effect.[33]



(XIX-31)

e. Cobefrine

Cobefrine, 1-(3,4-dihydroxyphenyl)-2-aminopropanol [3,4-$(HO)_2C_6H_3$-$CHOHCH(CH_3)NH_2$] is a homolog of Arterenol. It can be prepared from 3,4-dihydroxypropiophenone by a synthesis similar to that of epinephrine. Its most surprising property is its oral activity. The catechol structure found both in the hormone and in Cobefrine would favor the prediction that Cobefrine should be equally unstable as the hormone, since the *o*-dihydroxy arrangement of the latter had long been blamed for its inactivity on oral administration. This is, however, not the case. While a satisfactory explanation for this difference is still lacking, attention has been called to the increase in stability, and the oral activity conferred upon β-arylisopropylamines in general by the branching of the carbon chain α to the amino group.[34] The possibility that this is due to a resistance to destruction by dehydrogenases will be set forth below.

Cobefrine has found use as an analeptic.

f. Butanefrine

Butanefrine, 1-(3,4-dihydroxyphenyl)-2-aminobutanol (3,4-$(HO)_2C_6$-$H_3CHOHCH(C_2H_5)NH_2$), the next-higher homolog of Arterenol, can be synthesized by an analogous route. It has no centrally excitant action, and although only 0.014 times as active as epinephrine as a bronchodilator it relieves asthmatic attacks in doses one half larger than those of the hormone[35]; its toxicity is low. It is not a vasopressor but lowers diastolic pressure and increases the pulse rate; this is regarded as a desirable improvement of the circulation without additional tax on the heart.[36]

[32] Schaumann, *Arch. exp. Pathol.*, **160,** 127 (1931).
[33] Siegmund, Nash, and Granger, *J. Pharmacol. Exptl. Therap.*, **92,** 207 (1948).
[34] Hartung, Munch, Miller, and Crossley, *J. Am. Chem. Soc.*, **53,** 4149 (1931).
[35] Tainter, Pedden, and James, *J. Pharmacol. Exptl. Therap.*, **51,** 380 (1934).
[36] Suter and Ruddy, *J. Am. Chem. Soc.*, **66,** 747 (1944).

7. Benzedrine

Benzedrine (amphetamine, 1-phenyl-2-aminopropane, XIX-32) was prepared first by Edeleanu[37] by a Hofmann degradation of benzylmethylacetamide. Similar syntheses of scientific interest include the degradation of benzylmethylacetic acid (XIX-33) by the Curtius and Schmidt methods.[38]

$$\underset{\text{(XIX-33)}}{C_6H_5CH_2CH(CH_3)CO_2H} \rightarrow \underset{\text{(XIX-32)}}{C_6H_5CH_2CH(CH_3)NH_2}$$

These reactions have contributed materially to our understanding of molecular rearrangements since they may be carried out with optically active benzylmethylacetic acid; optical activity is largely preserved during the degradations.

The commercial synthesis of amphetamine (XIX-32) begins with phenylacetone (XIX-34) obtained by thermal dehydration and decarboxylation of phenylacetic acid. Phenylacetone is then subjected to the Leuckart reaction, a reductive amination with formamide, ammonium formate and formic acid. The formyl derivative (XIX-35) from this reaction is hydrolyzed with strong acid.

$$C_6H_5CH_2CO_2H + CH_3CO_2H \rightarrow \underset{\text{(XIX-34)}}{C_6H_5CH_2COCH_3} + CO_2 + H_2O$$

$$C_6H_5CH_2COCH_3 + HCO_2H + NH_3 \rightarrow \underset{\text{(XIX-35)}}{C_6H_5CH_2CHNHCHO}{\Big|}{CH_3} + H_2O$$

$$C_6H_5CH_2CHCH_3 + HOH \xrightarrow{H^+} C_6H_5CH_2CHNH_2 + HCOOH$$
$$\Big|\qquad\qquad\qquad\qquad\qquad\Big|$$
$$NHCHO\qquad\qquad\qquad CH_3$$
$$\text{(XIX-32)}$$

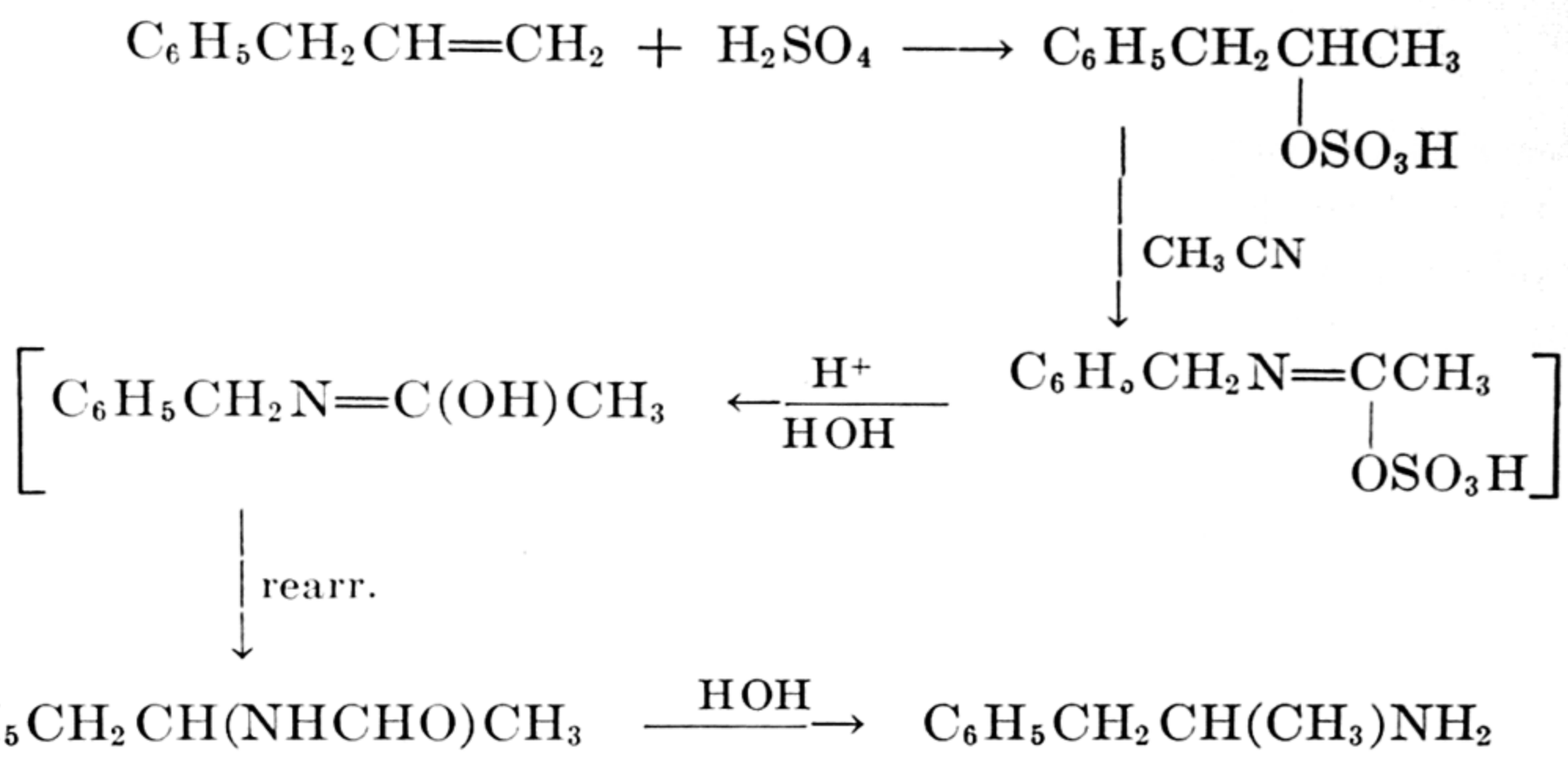
Reductive amination of phenylacetone in the presence of nickel catalyst and ammonia under pressure has also been used.

An interesting synthesis of amphetamine which promises to be applicable to similar compounds as well has been reported recently.[39] It involves the addition of acetonitrile to allylbenzene in the presence of sulfuric acid.

[37] Edeleanu, *Ber.* **20,** 616 (1887).

[38] Jones and Wallis, *J. Am. Chem. Soc.*, **48,** 169 (1926). Braun and Friehmelt, *Ber.*, **66,** 684 (1933). Wallis and Nagel, *J. Am. Chem. Soc.*, **53,** 2787 (1931).

[39] Ritter and Kalish, *J. Am. Chem. Soc.*, **70,** 4048 (1948).



The intermediate ester of sulfuric acid adds the nitrile which then rearranges to N-formylamphetamine from which the primary amine can be obtained by hydrolysis.

The important clinical uses of amphetamine were recognized by Alles,[40] and the drug was soon marketed under the brand name of Benzedrine. Later the *d*- and *l*-isomers were separated by optical resolution with tartaric acid.[41] The *d*-form (Dexedrine) is from two to four times more active a central stimulant than the racemic mixture; this is interesting because the *levo* form of many other compounds is the more active of two optical isomers. Amphetamine has less than 1/100th the vasopressor activity of epinephrine, but five to ten times its duration of action, and only about 1/70th its toxicity.

A widely appreciated physical property of Benzedrine is its volatility. It is the most useful vasoconstrictor derivative of phenethylamine which can be inhaled without special vaporizers, sprayers or "atomizers", and thus makes topical shrinking of congested nasal membranes a simple task.

Taken orally or parenterally, the main other therapeutic uses of amphetamine depend on its stimulation of the central nervous system. In laboratory animals, the analeptic effect of the drug can be observed by purposeless, random movements; they can be evaluated by suspending the cages on springs and connecting them to recording devices. In man, the tremendous "lift" amphetamine can give has been used for treatment of the depression by barbiturate; it has the added advantage that it increases the depressed circulation to the brain and thus helps to remove the narcotic. It is also preferred for the control of narcolepsy, a condition similar to

[40] Alles, *J. Pharmacol. Exptl. Therap.*, **32,** 121 (1927); **47,** 339 (1933). Alles and Prinzmetal, *ibid.*, **48,** 161 (1933). Compare Hartung and Munch, *J. Am. Chem. Soc.*, **53,** 1875 (1931).

[41] Nabenhauer, British Pat. **550,916** (1943).

petit mal epilepsy in which the patient may go through a dreamy, semi-unconscious condition several times each day.

The analeptic effect of Benzedrine has been utilized in psychotherapy to boost depressed personalities temporarily to a more normal state. Hesitant, undecided and tense people become decisive, energetic and calm under the influence of the drug, they overcome fatigue, and their intellect is cleared and stimulated. Depression due to psychoneuroses and alcoholism can often be successfully abolished, especially by Dexedrine.

The valuable effect of Benzedrine on the central nervous system has been explained on the basis of the ability of the drug to compete reversibly with other amines for the enzyme amine oxidase (XIX, Section V) in the brain. This enzyme dehydrogenates biogenic amines to imines which are subsequently hydrolyzed to carbonyl compounds and ammonia. The aldehydes inhibit and

$$RCH_2NH_2 \rightarrow RCH{=}NH \rightarrow RCHO + NH_3$$

depress normal functions. By occupying the enzyme, Benzedrine cuts down on the depressant effect of these metabolic products.[42]

A side-effect of Benzedrine which has been bent to a useful purpose is the control of gastric contraction by the drug. These contractions simulate hunger and tend to lead to over-eating. Amphetamine, and especially Dexedrine, have therefore been employed with some success as anorexics, i.e., antiappetite agents in obese individuals. Their most undesirable side action is promotion of wakefulness in patients in whom the prevention of normal sleep is not intended as a therapeutic measure.

8. Benzedrex

A valuable innovation in nasal shrinkers has recently been announced with the release of N-methyl β-cyclohexylisopropylamine, $C_6H_{11}CH_2CH(CH_3)NHCH_3$ (Benzedrex) as the active drug in inhalers.[43] This drug lacks the centrally stimulating properties of Benzedrine.

9. Mephentermine

This compound contains a doubly branched, quaternary carbon atom *alpha* to its secondary amino group ($C_6H_5CH_2C(CH_3)_2NHCH_3$). It can be used as a nasal shrinker but is only one-third to one-fourth as effective as Benzedrine in animals. It does not cause cerebral stimulation.[44]

[42] Mann and Quastel, *Biochem. J.*, **34,** 414 (1940).

[43] Ullyot, U. S. Pat. 2,454,746 (1948). Macko and Fellows, *Federation Proc.*, **8,** 318 (1949).

[44] Seifter, Eckfeld, and Abell, *Abstracts*, Meeting, Am. Chem. Soc., Atlantic City, N. J., Sept., 1949, p. 17 L.

10. Mescaline

The centrally excitant effect which can be used to advantage with amphetamine reaches excessive forms with the alkaloid mescaline (3,4,5-trimethoxyphenethylamine, 3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$, XIX-68), from the Mexican cactus, *Anhalonium Lewinii*.[45]

In small doses, it gives the illusion of geometrical and color phenomena and causes mental and muscular incoordination. Larger doses produce frenzied delirious states. The Southwestern and Mexican Indians are transposed to fanaticism in religious orgies in which peyote, a mescaline-containing concoction from the mescal buttons forms the ceremonial drink.

Mescaline produces schizophrenic states in normal individuals but does not accentuate the symptoms of schizophrenic patients. On the other hand, the isomeric 2,3,4-trimethoxyphenethylamine increases the excitement of schizophrenics but does not affect normal persons.

11. Pervitin

The N-methyl derivative of amphetamine, Pervitin (XIX-36) can be prepared from the primary amine by the Decker reaction, condensing it with benzaldehyde and condensing the benzal derivative with methyl sulfate. The quaternary salt is then alcoholyzed.

$$C_6H_5CH_2CH(CH_3)NH_2 \rightarrow C_6H_5CH_2CH(CH_3)N{=}CHC_6H_5$$
$$\rightarrow [C_6H_5CH_2CH(CH_3)\overset{+}{N}(CH_3){=}CHC_6H_5]CH_3SO_4^-$$
$$\xrightarrow{EtOH} C_6H_5CH_2CH(CH_3)NHCH_3$$

(XIX-36)

The effects of Pervitin are similar to those of Benzedrine, and the drug has been used in alcoholism. It is however, somewhat more toxic than amphetamine.[46]

The dextro isomer of Pervitin, called Methedrine, is used clinically for conditions similar to those treated with Dexedrine. It is also a valuable vasopressor agent following spinal anesthesia.[47]

12. Vonedrine

In contrast to Pervitin, its structural isomer Vonedrine (XIX-37), 2-phenyl-1-methylaminopropane ($C_6H_5CH(CH_3)CH_2NHCH_3$), is virtually devoid of analeptic action when used in therapeutic doses. On the other

[45] Henry, *The Plant Alkaloids*, 4th ed. Blakiston, Philadelphia, 1949.
[46] Golla, Blackburn, and Graham, *J. Mental Sci.*, **86,** 48 (1940).
[47] Yeakel and Seldon, *Anesthesiology*, **9,** 605 (1948).

hand, its toxicity (LD_{50} 65 mg./kg intravenously to rabbits)[48] is far smaller than that of Pervitin (MLD 17 mg./kg intraperitoneally to rats). It is rated as an excellent pressor agent. The synthesis of Vonedrine (XIX-37) consists of a Hofmann degradation of β-phenylbutyramide (XIX-38) to 1-amino-2-phenylpropane (XIX-39), conversion of the latter to the benzal derivative and hence to the methylamino compound by the Decker procedure.[49]

$$C_6H_5CH(CH_3)CH_2CONH_2 \xrightarrow[Br_2]{NaOH} C_6H_5CH(CH_3)CH_2NH_2$$

(XIX-38) (XIX-39)

$$\rightarrow C_6H_5CH(CH_3)CH_2N{=}CHC_6H_5 \xrightarrow[2.C_2H_5OH]{1.CH_3I} C_6H_5\underset{\displaystyle CH_3}{\underset{|}{CH}}CH_2NHCH_3$$

(XIX-37)

The corresponding primary amine can be prepared by Friedel and Crafts addition of allylamine to benzene.[50]

$$C_6H_6 + CH_2{=}CHCH_2NH_2 \rightarrow C_6H_5\underset{\displaystyle CH_3}{\underset{|}{CH}}CH_2NH_2$$

13. Paredrine

Paredrine, 2-(4-hydroxyphenyl)-isopropylamine (4-$HOC_6H_4CH_2CH(CH_3)NH_2$, XIX-40), is the *p*-hydroxy derivative of amphetamine. It is synthesized by reduction of *p*-methoxybenzyl-methyl ketoxime and subsequent hydrolysis of the methyl ether group with mineral acids.[51] Later, it was reinvestigated by Alles[52] in a systematic study of analogs of

$$p\text{-}CH_3OC_6H_4CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}NOH \longrightarrow CH_3OC_6H_4CH_2\underset{\displaystyle CH_3}{\underset{|}{CH}}NH_2$$

$$\longrightarrow HOC_6H_4CH_2\underset{\displaystyle CH_3}{\underset{|}{CH}}NH_2$$

(XIX-40)

[48] Warren, Marsh, Thompson, Shelton, and Becker, *J. Pharmacol. Exptl. Therap.*, **79,** 187 (1943).
[49] Graham, Cartland, and Woodruff, *Ind. Eng. Chem.*, **37,** 149 (1945).
[50] Weston, U. S. Pat. 2,444,518 (1948).
[51] Rosenmund, Mannich, and Jacobsohn, German Pat. 243,546 (1912).
[52] Alles, *J. Pharmacol. Exptl. Therap.*, **47,** 339 (1933). Alles and Prinzmetal, *ibid.*, **48,** 161 (1933). Alles and Knoefel, *Arch. intern. pharmacodynamie*, **47,** 96 (1934).

Benzedrine. Paredrine is 1–2% as active as epinephrine as a pressor amine; its toxicity is remarkably low, and it is very stable. In contrast to amphetamine, it has practically no effect on the central nervous system and can be used in certain diseases of the circulatory system when central effects are to be avoided. It shows too little activity as an anti-appetite agent as well as a bronchodilator in clinical medicine to be considered for these uses but it has a stronger mydriatic action than any other sympathomimetic amine. Its main use is in ophthalmology, in combination with atropine or homatropine. These mixed solutions approach the ideal condition for complete dilatation of the pupil of the eye without irritation in a short time, and the normal function of the eye is restored more rapidly than after atropine or homatropine alone.

14. Veritol

The N-methyl derivative of Paredrine, 2-(4-hydroxyphenyl)-N-methylisoproplyamine (4-$HOC_6H_4CH_2CH(CH_3)NHCH_3$) is used in Europe under the name of veritol. It is essentially similar to Paredrine and, although tested briefly under the name Paredrinol, has not found much use in the United States. In its circulatory effects, constriction of the veins seems to be pronounced while arterial constriction is the more common property of sympathomimetic amines in general.[53] Its use in glaucoma, a disease of the eye with intraocular pressure, has been suggested.[54]

15. Orthoxine

The methyl ether of the *o*-isomer, 2-(2-methoxyphenyl)-N-methylisopropylamine (Orthoxine) has only about one-thousandth the pressor activity of epinephrine, one twentieth its bronchodilator action, and no stimulant action on the central nervous system.[55]

16. Tyramine

Tyramine (uteramine, systogene, *p*-hydroxyphenethylamine, 4-$HOC_6H_4CH_2CH_2NH_2$) has 0.01–0.05 the pressor activity of epinephrine. Its toxicity is less than 1/13000th that of the hormone, and its action lasts twice as long. Nevertheless, it is no longer widely used. It occurs in ergot but is usually manufactured by decarboxylating tyrosine, obtained from the hydrolysis of silk refuse, in a high-boiling solvent, for instance, fluorene. The name uteramine was to indicate its motoric action on the

[53] Reis, *Quart. J. Exper. Physiol.*, **30,** 1 (1940).
[54] Schmidt, *Klin. Monatsbl. Augenheilkunde*, **100,** 429 (1941); *Chem. Abstr.*, **36,** 4199 (1942).
[55] Graham and Kuizenga, *J. Pharmacol. Exptl. Therap.*, **94,** 150 (1948).

uterus; it still finds limited application as an initiator of uterine movements in deliveries.[56]

17. Hordenine

Hordenine (anhaline), *p*-hydroxy-N,N-dimethylphenethylamine (XIX-41) may be prepared from tyramine by way of its quaternary salt; the methochloride is then decomposed by distillation under reduced pressure.

$$p\text{-}HOC_6H_4CH_2CH_2NH_2 \xrightarrow{3\ CH_3Cl} p\text{-}HOC_6H_4CH_2CH_2\overset{+}{N}(CH_3)_3Cl^- \longrightarrow p\text{-}HOC_6H_4CH_2CH_2N(CH_3)_2$$

(XIX-41)

Other syntheses have also been reported. Hordenine is found naturally as the alkaloid of malt germs.[57] It is a rather non-toxic vasopressor and has found limited application in the symptomatic treatment of diarrhea and dysentery since, like other compounds in this series, it inhibits peristalsis.

18. Epinine

Epinine, 3,4-dihydroxy-N-methylphenethylamine (XIX-47) has been known for forty years.[58] After a period of comparative neglect it has recently experienced a renaissance of usefulness. It is synthesized from eugenol, or can be obtained by a series of degradative reactions from papaverine.

The synthesis from eugenol methyl ether (XIX-42) leads through homoveratraldehyde (XIX-43), the oxime of which is reduced to homoveratrylamine (XIX-44). The latter can be obtained more conveniently by condensing veratraldehyde (XIX-45) with nitromethane, and reducing the resulting β-nitrostyrene derivative (XIX-46) with lithium aluminium hydride. The N-methyl derivative of homoveratrylamine is cleaved to Epinine (XIX-47) with the aid of hydrobromic acid. (See Fig. 2.)

The degradation of papaverine (XIX-48) through the key intermediate, 6,7-dimethoxy-N-methyl-3,4-dihydroisoquinolinium chloride (XIX-52) offers an interesting example of using a valuable alkaloid as a synthetic starting material for a not too closely related drug. Papaverine is reduced to tetrahydropapaverine (XIX-49), and the benzoyl derivative of the latter (XIX-50) is oxidized and subsequently hydrolyzed to a mixture of

[56] Waser, *Helv. Chim. Acta*, **8,** 758 (1925).
[57] Winterstein-Trier, *Die Alkaloide*. Bornträger, Berlin, 1931, p. 125–126.
[58] Pyman, *J. Chem. Soc.*, **95,** 1266, 1610 (1909); **97,** 264 (1910). Burroughs Wellcome and Co., *Apotheker Z.*, **26,** 779 (1911); *Chem. Zentr.*, 1911, II, 1263.

veratraldehyde (XIX-45) and 6,7-dimethoxy-3,4-dihydroisoquinoline (XIX-51). This cyclic amine is quaternized (XIX-52), the methochloride

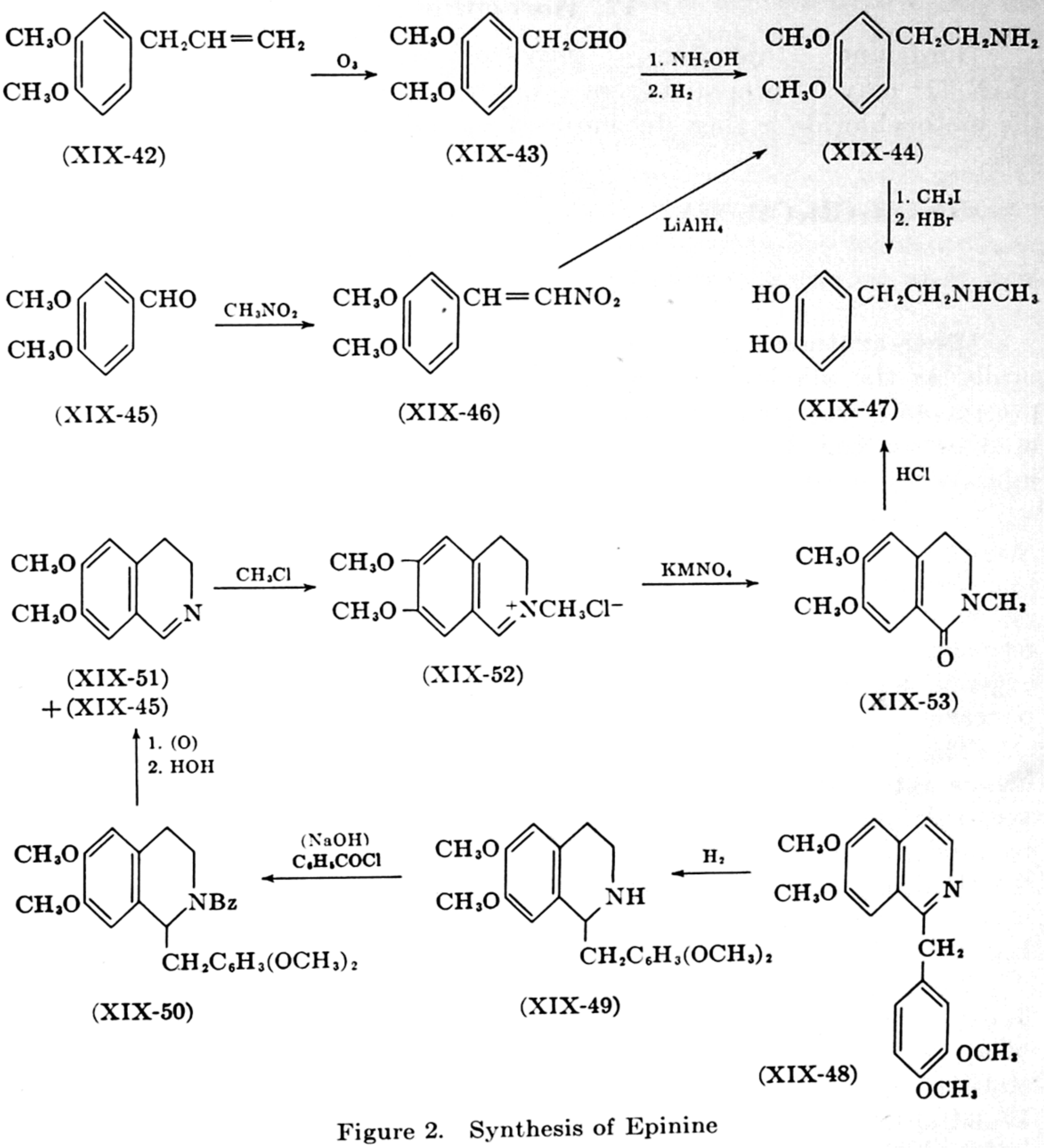


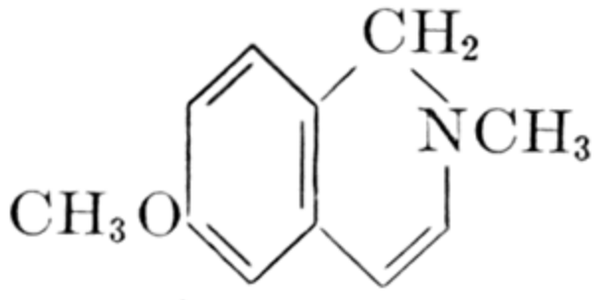
Figure 2. Synthesis of Epinine

is oxidized in alkaline medium to 6,7-dimethoxy-2-methyl-1-isoquinolone (XIX-53) and the latter is cleaved to Epinine with hydrochloric acid at 175°.

Epinine exhibits one twelfth the pressor activity of L-epinephrine. Its motor effect on the gravid uterus is especially pronounced,[59] and it has been used considerably in gynecology.

19. Isoquinoline Derivatives

The incorporation of the ethylamine side chain in an isoquinoline ring usually produces pressor compounds. Many 1,2,3,4-tetrahydroisoquinoline derivatives possess a pressor activity greater than that of the corresponding phenethylamines. In almost all cases, toxicity is increased even more than the useful pharmacodynamic behavior. However, depressors are encountered also among the hydrogenated isoquinolines. 6-Methoxy-N-methyl-1,2-dihydroisoquinoline (XIX-54) has been reported to cause a marked and sustained fall in blood pressure in hypertensive dogs. It may be that this compound should be interpreted as a cyclic derivative of benzylamine rather than phenethylamine.



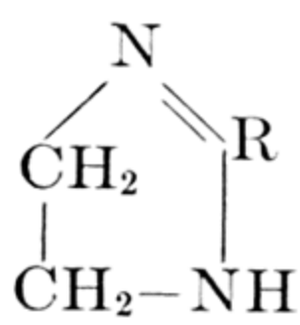
(XIX-54)

20. Priscoline and Privine

Similar differences in the vasomotoric behavior of another series of related compounds in which the ethylamine chain has become part of a heterocyclic ring have been observed among 2-aralkyl substituted imidazolines.[60] Guided by the thought that nature produces many physiologically active alkaloids, amino acids and biogenic amines containing the



(XIX-55)

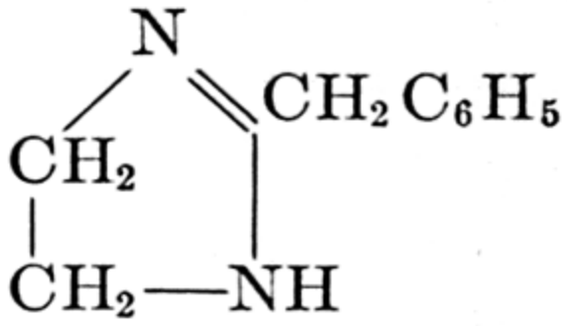


(XIX-56)

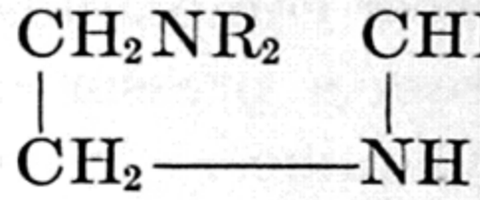
imidazole ring (pilocarpine, histidine, histamine), simple derivatives of imidazole (XIX-55) and imidazoline (XIX-56) had been tested repeatedly for pharmacological activity.

[59] Hjort, *J. Pharmacol. Exptl. Therap.*, **52,** 101 (1934).
[60] Scholz, *Ind. Eng. Chem.*, **37,** 120 (1945). Hartman and Isler, *Arch. exp. Path.*, **192,** 141 (1939).

Several of the latter in which R = benzyl or hydrogenated benzyl showed definite vasodilator and hypotensive action in laboratory animals and stimulated further research in this field. It is noteworthy that 2-benzylimidazoline, Priscoline (XIX-57) can be thought of as a substituted phenethylamine (XIX-58); this analogy may serve as a basis of understanding its vasomotoric properties.



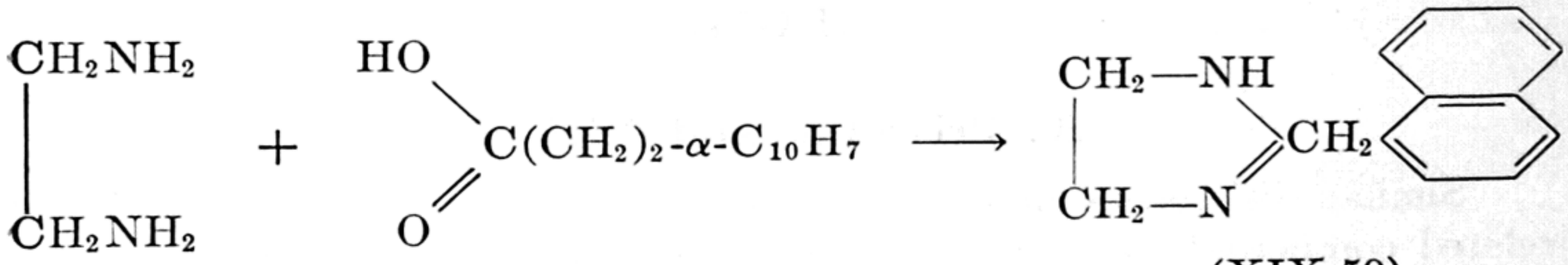
(XIX-57)



XIX-58)

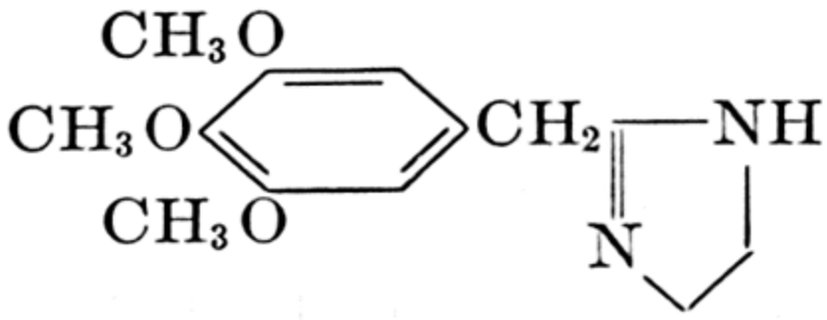
Surprisingly, 2-(α-naphthylmethyl)imidazoline (Privine, XIX-59) is not a vasodilator like the benzyl derivative (XIX-57), but a powerful hypertensive vasoconstrictor of low toxicity. It also lowers body temperatures. This effect seems to be connected with the presence of a cyclic —C—C—N= structure.

Privine is synthesized by heating ethylenediamine and 3-(α-naphthyl) propionic acid at 280°.

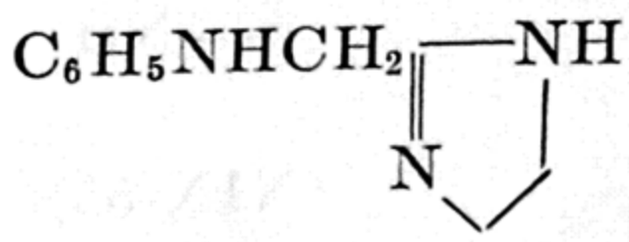


(XIX-59)

Introduction of phenolic hydroxyl or of methoxyl groups into the benzene ring of Priscoline reverses the hypotensive qualities of this drug. The 3,4,5-trimethoxy derivative (Phedrazine, XIX-60) is a typical hypertensive agent.



(XIX-60)



(XIX-61)

Interposition of an imino group between the aromatic ring and the methylene group leads to a derivative of phenylethylenediamine. The drug Otrivine (2-anilinomethylimidazoline, XIX-61) has intensive and long-lasting pressor activity.

III. PHARMACOLOGICAL PROPERTIES AND THERAPEUTIC USES[61, 62]

The mode of action of at least some adrenergic amines may be explained on the basis of their relation to the sympathetic mediator, sympathin. These drugs either protect this mixture of epinephrine and norepinephrine from destruction by competing with it for the same detoxifying enzyme, or they promote secretion of the mediator at the neuronic synapse. The symptomatic relief brought about by adrenergic drugs is the ultimate result of these enzymatic reactions, and influences the physiological behavior of the glands and muscles at the endings of the nerves whose impulses are affected.

1. Effects on Blood Pressure

a. Methods and Applications

The most significant and dramatic changes brought about by sympathomimetics are in the condition of the circulatory system. Blood pressure is the composite expression of many components; among them is the pressure within the vascular systems (blood vessels) which is maintained by the contraction of the left heart ventricle. Contraction of the vessels (vasoconstriction) will tend to raise blood pressure (produce hypertension); vasodilation causes a drop in pressure (hypotension). Systolic blood pressure is the maximum pressure occurring at the moment of ventricular contraction. Diastolic pressure is the one immediately preceding the systole. The difference between systolic and diastolic pressure is called pulse pressure.

Blood pressure is measured by manometric or membrane type reading devices both in animals and man. The membrane devices are often composed of two facing membranes which act as electrical condensers, and as they move to and from each other under the influence of the changing blood pressure, the changes are amplified and recorded.

The most common practical device for measuring the pulse pressure works by the asculatory method. It consists of an inflatable cuff which is wrapped around the upper arm and is connected to a manometer. The cuff is inflated by a rubber bulb until the pressure on the arm is high enough to obliterate the pulse. Then a stethoscope is applied over the artery above the inner elbow and the air of the inflated cuff is released slowly through

[61] Tainter, *Ind. Eng. Chem.*, **37,** 138 (1945).
[62] Gold, *Ind. Eng. Chem.*, **37,** 117 (1945).

a needle valve until the pulse becomes just audible again. At this moment, the manometer is read; the pressure corresponds to the systolic pressure overcoming the gradually falling air pressure. A few moments later, the last sound is heard, representing the diastolic pressure; below this there are no sounds, just as nothing can be heard with a stethoscope when placed over a peripheral artery unless pressure is applied.

Measuring the pressure of the blood is actually of minor importance pharmacologically than measuring the volume of flow of blood. By decreasing the size of blood vessles (vasoconstriction) a sympathomimetic amine may increase the pressure while cutting down the volume of blood flowing through the constricted vessels. Since the tissues need a certain amount of blood as a vehicle for water, oxygen and metabolites, and to remove waste, the heart will be taxed unduly under these circumstances. Pulse rate may rise unnecessarily together with pulse pressure, but there exist cardiac conditions where the increase of the ability of the heart to empty its blood supply under the influence of a sympathomimetic drug is of advantage. The most common conditions which require raising of blood pressure without other stimulatory effects are primary shock, and the fall of pressure so often encountered during anesthesia. Paradoxically, therapeutic results in shock have been disappointing since the blood vessels are already constricted nearly to capacity. Consequently, little or no pressor response is elicited on administration of a vasoconstrictor agent.

Orthostatic hypotension is a condition in certain patients who experience lowered blood pressure when they stand or sit, and may faint. Neosynephrine, Paredrine and some related vasopressors are capable of restoring normal blood pressure without acceleration or increase of the work of the heart. Ephedrine and epinephrine also provide a rise in systolic pressure, and ephedrine especially produces a prolonged action. Both drugs, however, give rise to anxiety symptoms.

The cardiac stimulating action of epinephrine and its congeners is of greatest value if weak blood vessels, unable to contract properly, or a heart poisoned by an anesthetic are the cause of heart failure. A qualitative variation of this effect is attained by several other chemically unrelated drugs, the digitalis glycosides, and certain stimulants, especially caffeine, theophylline, alkyl nitrites, quinidine and others. These types are discussed in other chapters.

b. Essential Hypertension

Constant maintenance of abnormally high blood pressure—essential hypertension—is the cause of an ever-increasing number of diseases and death among elderly individuals. The cause of this condition is unknown but present evidence points to the inability of a damaged kidney to de-

aminate or otherwise deactivate pressor amines, especially epinephrine, which are produced by decarboxylation of proteinogenous amino acids. Other explanations envisage an unbalance between epinephrine and norepinephrine as the possible cause of hypertension.[62a]

c. Potentiation of Pressor and Depressor Effects

It has long been known that *small* intravenous doses of epinephrine cause a fall of arterial pressure in the anesthetized dog. The expected rise in pressure follows the injection of larger doses, and the animal immediately tends to restore homeostasis by setting into motion the so-called compensatory or buffer mechanisms. They include slowing of the heart, and extension of the walls of the blood vessels by reflex action. The compensatory reflexes are led along autonomic pathways, and are prevented by any agent which blocks autonomic impulses. It is an elegant confirmation of the chemical theories of nervous transmission that tetraethylammonium chloride, a typical autonomic blocking agent, *potentiates* the pressor effect of epinephrine by preventing those reflexes by which the animal tries to overcome the increase in blood pressure.

For the same reason, drugs which lower blood pressure, will evoke compensatory mechanisms tending to offset this change. Again, tetraethylammonium ions will block these reflexes, and thereby potentiate the depressor effect of the drug.[63]

d. Local Vasoconstriction

Specific vascular areas in which alteration of blood volumes are of therapeutic value are the kidney and the nasal mucosa. Insufficient flow of blood through the kidney is one of the results of high blood pressure. In the nasal membranes, expanded blood vessels cause turgescence, and vasoconstriction opens up the nasal passages and relieves difficulties in breathing.

None of the presently available amines offer any special advantage for this purpose; amphetamine has the advantage of being volatile, and it has constituted the active ingredient in a popular nasal inhaler (Benzedrine inhaler). On the other hand, some other amines which have to be used as nose drops, especially Neosynephrine, Propadrine and Paredrine, exert less central stimulation. Several volatile analogs of amphetamine lacking central action have been introduced recently, especially β-cyclohexylisopropylmethylamine (Benzedrex).

The prolongation of the effect of local anesthetics by vasoconstriction has been discussed in Chapter VIII. Cocaine is in itself a vasoconstrictor,

[62a] Nickerson, *Am. J. Med.*, **8,** 342 (1950).
[63] Moe, *J. Am. Med. Assoc.*, **137,** 1115 (1948).

but most synthetic local anesthetics require epinephrine, or sometimes a non-excitatory synthetic pressor amine to avoid de-localization by the circulating blood.

Just as cocaine combines local anesthetic and vasoconstrictor properties, some pressor amines exhibit local anesthetic and even analgetic activity (see page 345). This has been utilized in the case of the volatile 2-amino-6-methylheptane ($CH_3CH(NH_2)(CH_2)_3CH(CH_3)CH_3$). When this aliphatic amine is inhaled from a small tube (Oralator), it seems to anesthetize topically inflamed and irritated surfaces in the air passage way, and has thus been found of value to sooth a sore throat, and to counteract cough due to colds.

Other aliphatic amines and amino alcohols, for instance 2-methylamino-6-methylheptanol-6, ($CH_3NHCH(CH_3)(CH_2)_3C(CH_3)_2OH$), have principally vasopressor properties. 2-Methylaminoheptane ($CH_3NHCH(CH_3)(CH_2)_4CH_3$, Oenethyl) is a slow but sustained vasopressor useful in the treatment of hypotension resulting from spinal anesthesia.

2-Aminoheptane (Tuamine) has been introduced for similar purposes.[64] The relationships of chemical structure and pressor activity of aliphatic amines will be reviewed in this Chapter, Section VI-2.

2. Effect on Bronchospasm

a. General

The constriction of the swollen and dilated bronchial vessels in bronchospasm and asthma could perhaps be classified as a local vasoconstrictor effect of the sympathomimetic amines. Indeed, epinephrine is able to relieve bronchial asthma in very small doses (0.25 mg. or less), but until recently epinephrine has stood virtually alone in this action. Other similar compounds, especially Paredrine (XIX-40) also exert a strong bronchodilator and vasoconstrictor effect in experimental asthma but are practically ineffective in the human disease. The anxiety symptoms caused by epinephrine add to the discomfort of the patient and have made this compound a drug of necessity rather than of choice. Ephedrine (XIX-24) can be taken by mouth ir contrast to epinephrine which is administered parenterally. But although the bronchodilator effect of ephedrine is more sustained, it does not come near the quality of relief obtained with epinephrine.

The mechanism of bronchodilator action is not quite clear. Constriction of the bronchial blood vessels is undoubtedly a major contributing factor, since the hormone Pituitrin, known to constrict blood vessels in

[64] Rohrmann and Shonle, *J. Am. Chem. Soc.*, **66,** 1516 (1944).

general, can control asthmatic attacks. Relaxation of the spastic bronchial muscles may be another immediate effect.

The sympathetic innervation of the bronchi inhibits contraction of the bronchial muscles, and stimulation of these nerves by drugs relaxes the bronchi.

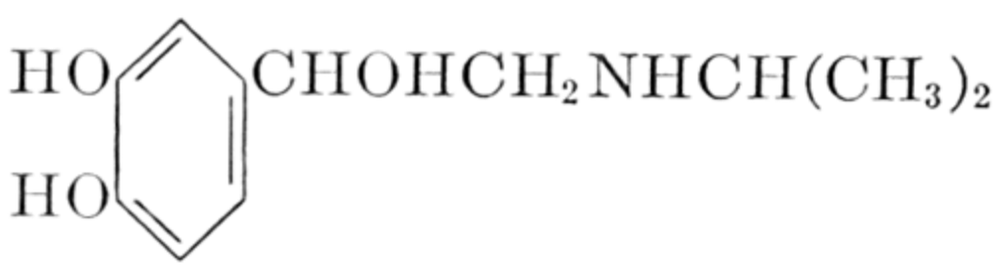
It seems that epinephrine, hitherto the supreme though certainly not the ideal drug used in this condition, has a specific affinity for bronchial vessels which the much less effective analogous compounds do not possess.

b. Isuprel

A re-investigation of Isuprel [β-(isopropylaminomethyl)-3,4-dihydroxybenzyl alcohol, XIX-62] which had been known for years under the name of aludrin demonstrated that this derivative of Arterenol (XIX-2) exhibits



(XIX-2)



(XIX-62)

a surprising type of activity. Instead of raising blood pressure, it lowers this function; in spite of its catechol structure, it is active orally like Cobefrine. However, when administered orally, that is, absorbed throughout the system, it causes pounding of the heart. This can be avoided by applying the drug topically to the bronchies by inhaling it as an aerosol. This mode of administration brings out the most valuable property of Isuprel: it is a powerful though shortlasting bronchodilator.[65] Other Arterenol derivatives, especially the N-*n*-butyl and the cyclopentylamino homologs, also have strong bronchodilator activity but do not rival Isuprel in usefulness.[66]

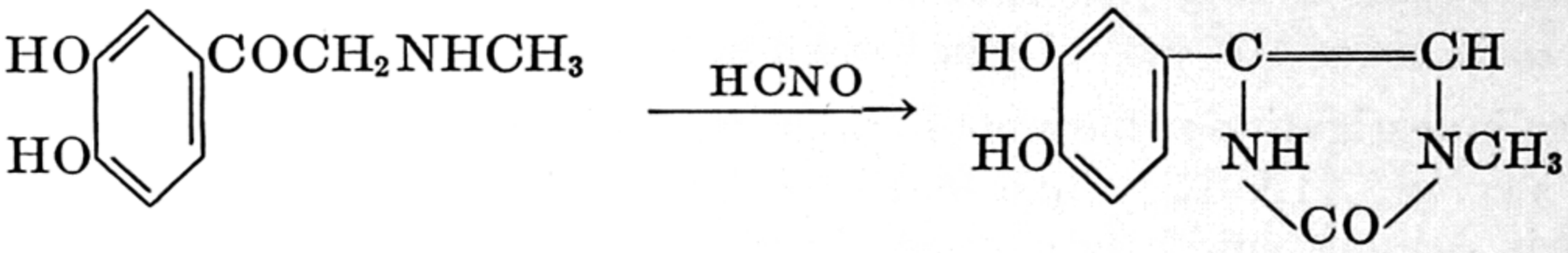
c. Derivatives of 1-Phenylethylenediamine

A series of potent bronchodilators has been discovered among compounds in which the alcoholic hydroxyl of the Arterenol type is replaced by a primary amino group. The most effective dilator which combines

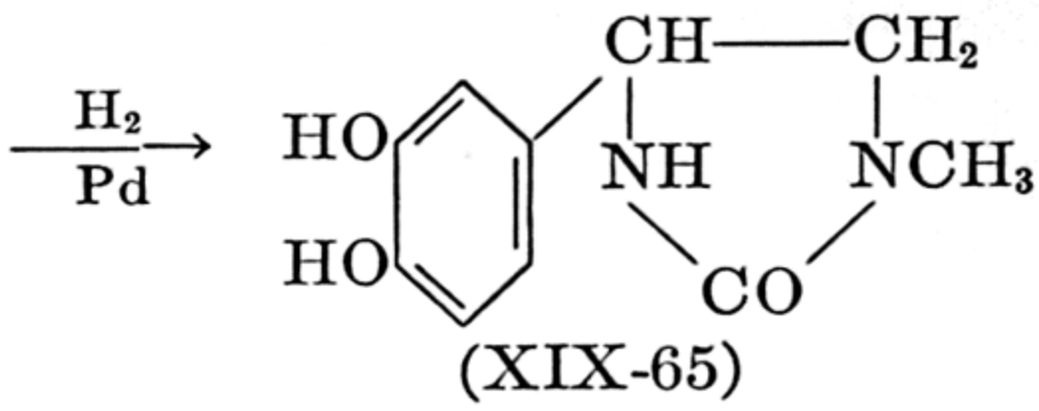
[65] Siegmund, Granger, and Lands, *J. Pharmacol. Exptl. Therap.*, **90,** 254 (1947). Corrigan, Langermann, and Moore, *J. Am. Chem. Soc.*, **71,** 530 (1949).

[66] Isuprel should not be confused with the old drug isopral (trichloroisopropyl alcohol, $Cl_3CCHOHCH_3$) which was patented as a hypnotic by Farbenfabrieken vorm. F. Bayer and Co., German Pat. 151,545 (1903). Likewise the older German name of Isuprel, Aludrine, might be confused with the abandoned hypnotic aleudrin (α,α′-dichloroisopropyl carbamate, $H_2NCOOCH(CH_2Cl)_2$) which was patented by Beckmann, German Pat. 271,737 (1911).

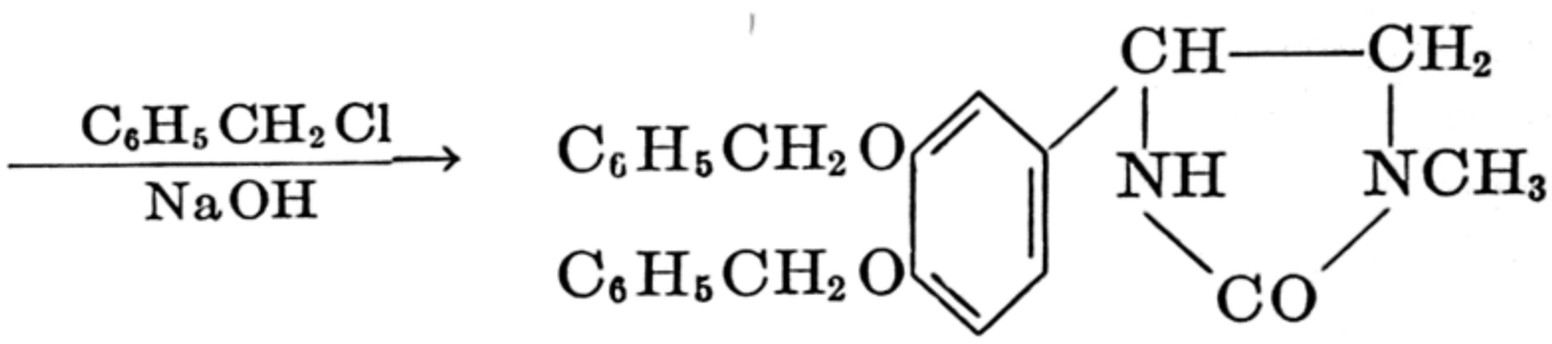
with this property low pressor activity (10% of epinephrine) is 1-(3,4-dihydroxyphenyl)-1-amino-2-methylaminoethane (XIX-63). It was synthesized from adrenalone (XIX-20).[67] This starting material yielded, with potassium cyanate, the imidazolone (XIX-64) which was hydrogenated to the corresponding imidazolidone (XIX-65). This was benzylated protectively (XIX-66) and then hydrolyzed to the diamine (XIX-67) by heating with ethanolic sodium hydroxide solution. The benzyl ether groups were finally removed as toluene by hydrogenation.



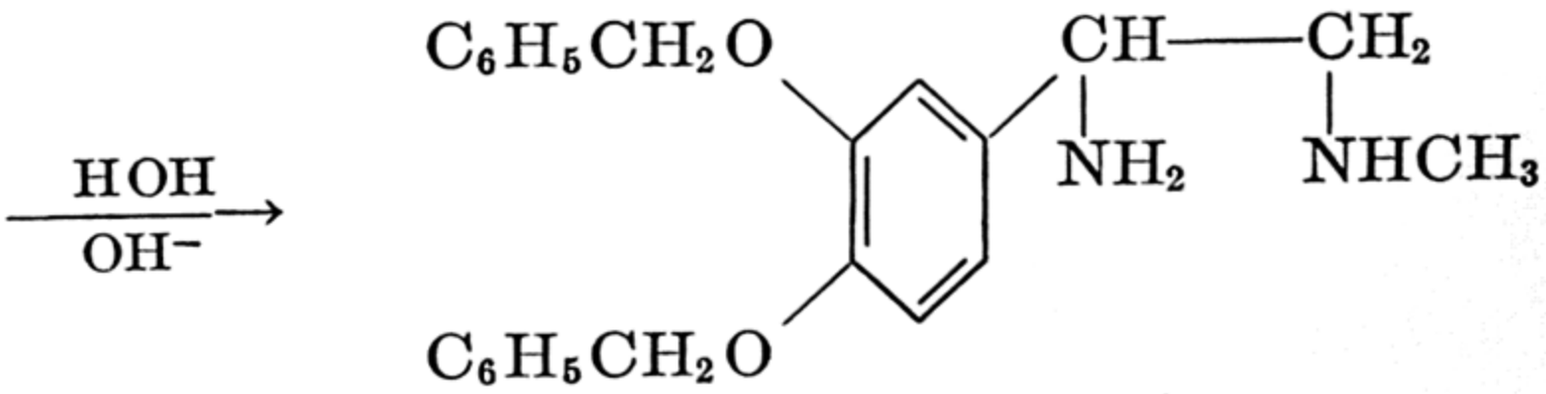
(XIX-20) (XIX-64)



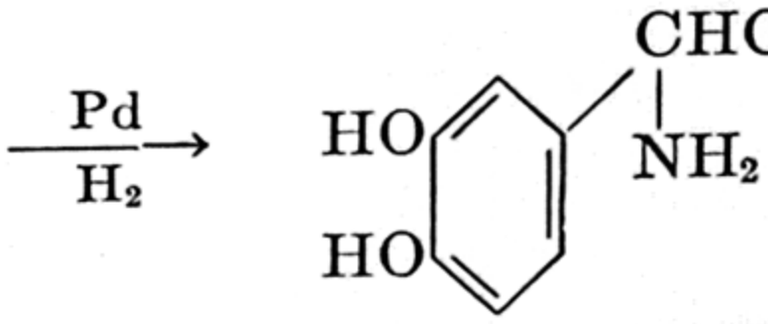
(XIX-65)



(XIX-66)



(XIX-67)



(XIX-63)

Although sympathomimetic amines can bring about maximum relaxation of spastic bronchial muscles, they cannot be classified with the true antispasmodics in the traditional sense. The antispasmodic drugs are

[67] Duschinsky, Dolan, Randall, and Lehmann, *J. Am. Chem. Soc.*, **69**, 3150 (1947).

concerned with the functioning of cholinergic nerve fibers, and they interfere with cholinergic overstimulation or analogous conditions at the receptor organ. The adrenergic amines, on the other hand, superimpose on parasympathetic stimulation their own powerful and opposite effect and thereby relax spastic involuntary muscles.

IV. ANALEPTIC EFFECTS

Some of the sympathomimetic amines, especially those with a 1-phenyl-2-aminopropane structure (amphetamine, ephedrine, Paredrine, etc.) stimulate the central nervous system. They may be classified broadly as analeptics (see Chapter XII) although their usefulness extends far beyond the lightening of narcosis which is the main purpose of analeptic drugs. A discussion of their effects which have been so helpful to the psychotherapist has been presented as part of the description of the most important analeptic of this series, amphetamine (Benzedrine) (page 310).

V. ENZYMATIC INACTIVATION OF PHENETHYLAMINES

The relatively simple chemical structure of the pressor amines and other autonomic drugs, and the profound changes in physiological symptoms brought about by small alterations of their molecules, has tempted many biochemists to study the possible common denominators of these compounds. It is not yet understood how any of the pressor amines react with cell chemicals, especially with enzymes, and although some investigators have speculated about the atomic, and even electronic, details of such reactions our concept of the structure of proteins is much too loose to permit an adequate interpretation of the overall symptomatic observations. Nevertheless, we can gather some information about the biochemical fate of the phenethylamines from *in vitro* studies of their behavior towards enzymes, and from an analysis of their metabolic products in living organs. This information offers the best contemporary approach to the fundamental understanding of the reaction of these simple drugs *in vivo*. Moreover, the effect of substituents, especially alcoholic and phenolic hydroxyl as well as small alkyl groups can be plotted in a surprisingly regular manner against the variations in pharmacodynamic properties in this series.

1. In vitro Studies

In vitro studies would have been more reliable if the enzymes had been homogeneous in all cases. The experimental difficulties involved in the purification of enzyme preparations have not made this possible in most cases. Diffusion of organs by the drug, or incubation of the drug solution with more or less purified enzyme concentrates have been the

rule in these experiments. It has therefore not always been possible to ascertain whether differences in the degradation of chemically similar drugs are due to the interaction with the same individual biocatalyst.

Primary carbinamines are deaminated in neutral or slightly acid solution under the influence of the enzyme monoamine oxidase,[68] according to the equations:

(*a*) $$RCH_2NH_3^+ + O_2 \rightarrow RCH{=}NH_2^+ + H_2O_2$$

(*b*) $$RCH{=}NH_2^+ + HOH \rightarrow RCHO + NH_4^+$$

Proof of this reaction is obtained readily by determining the ammonia and the rate of its formation by the Warburg technique, and isolating the aldehyde as the hydrazone or bisulfite addition compound in nearly quantitative yield by adding the necessary reagents to the incubated mixture. If this is not done, the aldehyde may become the substrate of aldehyde mutase,[69] an enzyme which disproportions it to the corresponding acid and alcohol:

$$2\ RCHO \rightarrow RCOOH + RCH_2OH$$

The rate of deamination is determined by the character of the group R. If R is an unbranched aliphatic chain, the rate is often high. Branching ($RR'CHCH_2NH_2$) slows it down, and if the carbon atom β to the amino group becomes quaternary ($RR'R''CCH_2NH_2$) deamination usually is not accomplished even if the alkyl groups are methyl.

Secondary methylamino compounds are more rapidly deaminated than the corresponding primary amines, methylamine being evolved.

$$RCH_2NHCH_3 + O_2 + HOH \rightarrow RCHO + NH_2CH_3 + H_2O$$

This increase in rate holds even for compounds with highly branched β-carbon atoms; $C_6H_5C(CH_3)_2CH_2NHCH_3$ is deaminated slowly, $C_6H_5C(CH_3)_2CH_2NH_2$ not at all. Amine oxidase does not touch N-ethylamino compounds ($C_6H_5CH_2CH_2NHC_2H_5$), and if the nitrogen atom is tertiary ($C_6H_5(CH_2)_2NR_2$), no deamination takes place either, regardless of the size of the alkyl groups.

Introduction of a secondary alcohol group ($C_6H_5CHOHCH_2NH_2$) somewhat decreases the rate of deamination; branching at the same carbon atom makes tertiary alcohols ($C_6H_5CR(OH)CH_2NH_2$) refractory to amine oxidase.

Phenolic primary carbinamines with amino or methylamino groups are among the most rapidly deaminizable substrates of monoamine oxidase

[68] Sumner and Somers, *Chemistry and Methods of Enzymes*. Academic Press, New York, 1943, p. 269.

[69] Pugh and Quastel, *Biochem. J.*, **31**, 286 (1937).

in vitro. Their behavior *in vivo* will be discussed below. Other nuclear substituents of less polar character have a less pronounced effect on the rate of deamination. One or two methyl groups in the ring do not affect materially the reactivity of the respective side chain. Nuclear fluorine, on the other hand, usually causes a drop in the rate of deamination.[70]

In sharp contrast to the primary carbinamines, the isomeric secondary carbinamines in which the carbon atom carrying the amino group is branched ($RCHR'NH_2$) are not affected by monoamine oxidase. Thus isopropylamine ($CH_3CH(CH_3)NH_2$), phenylisopropylamine ($C_6H_5CH_2CH(CH_3)NH_2$), ephedrine ($C_6H_5CHOHCH(CH_3)NHCH_3$), and Cobefrine ($3,4\text{-}(HO)_2C_6H_3CHOHCH(CH_3)NH_2$) are not altered by this enzyme. Nevertheless, these compounds combine with monoamine oxidase to loose complexes which dissociate again reversibly without a change in the structure of the amine. The rates of dissociation of several amines have been measured, k for phenylisopropylamine, for instance, being 4×10^{-4}. But because the secondary carbinamines combine with the enzyme, they prevent other amines from attaining a place at its reactive positions.

2. In vivo Studies

The detoxication of pressor amines by monoamine oxidase in the living animal follows only partly analogous pathways as under *in vitro* conditions. The purpose of monoamine oxidase is apparently to dispose of the natural phenethylamine derivatives such as tyramine (XIX-10). The more the structure of an amine deviates from that of the naturally occuring ones, the less effectively will it be destroyed by the enzyme. Both the acid and the alcohol formed by disproportionation of the aldehyde have been isolated from the *in vivo* deamination of several primary carbinamines.[71] Since monoamine oxidase is found in many mammalian

$$\underset{\text{(XIX-10)}}{HOC_6H_4(CH_2)_2NH_2} \xrightarrow[\text{Oxidase}]{\text{Amine}} HOC_6H_4CH_2CHO + NH_3$$

Aldehyde Mutase

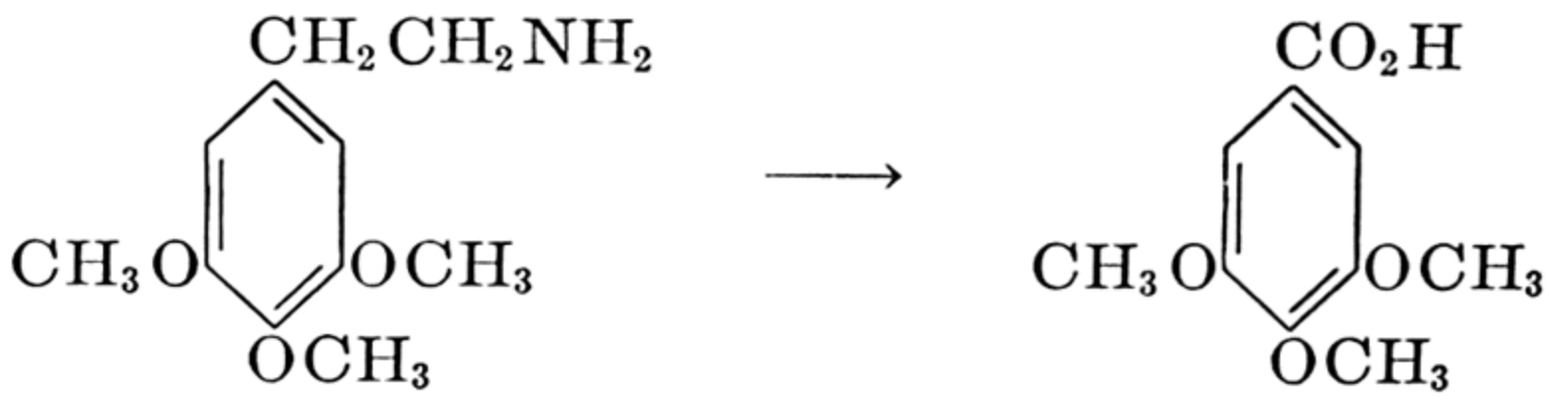
$$HOC_6H_4CH_2CO_2H + HOC_6H_4CH_2CH_2OH$$

tissues, especially in the liver, it is most probably the enzyme catalyzing the deamination of phenethylamines, phenylethanolamine and even aliphatic primary carbinamines such as isoamylamine. The irreversible de-

[70] Beyer and Morrison, *Ind. Eng. Chem.*, **37,** 143 (1945).
[71] Guggenheim and Löffler, *Biochem. Z.*, **72,** 325 (1916).

toxication of these drugs is the cause of the short duration of their pressor activity.

Some primary carbinamines whose structure bears less resemblance to proteinogenous amines may be excreted unchanged, or partly unchanged by some mammals which do not provide sufficient monoamine oxidase. Mescaline (XIX-68), for instance, is deaminated, and then oxidized to 3,4,5-trimethoxybenzoic acid in the dog or the rabbit,[72] but not altered extensively in man.[73] Phenolic carbinamines are degraded by more complex routes (see below).



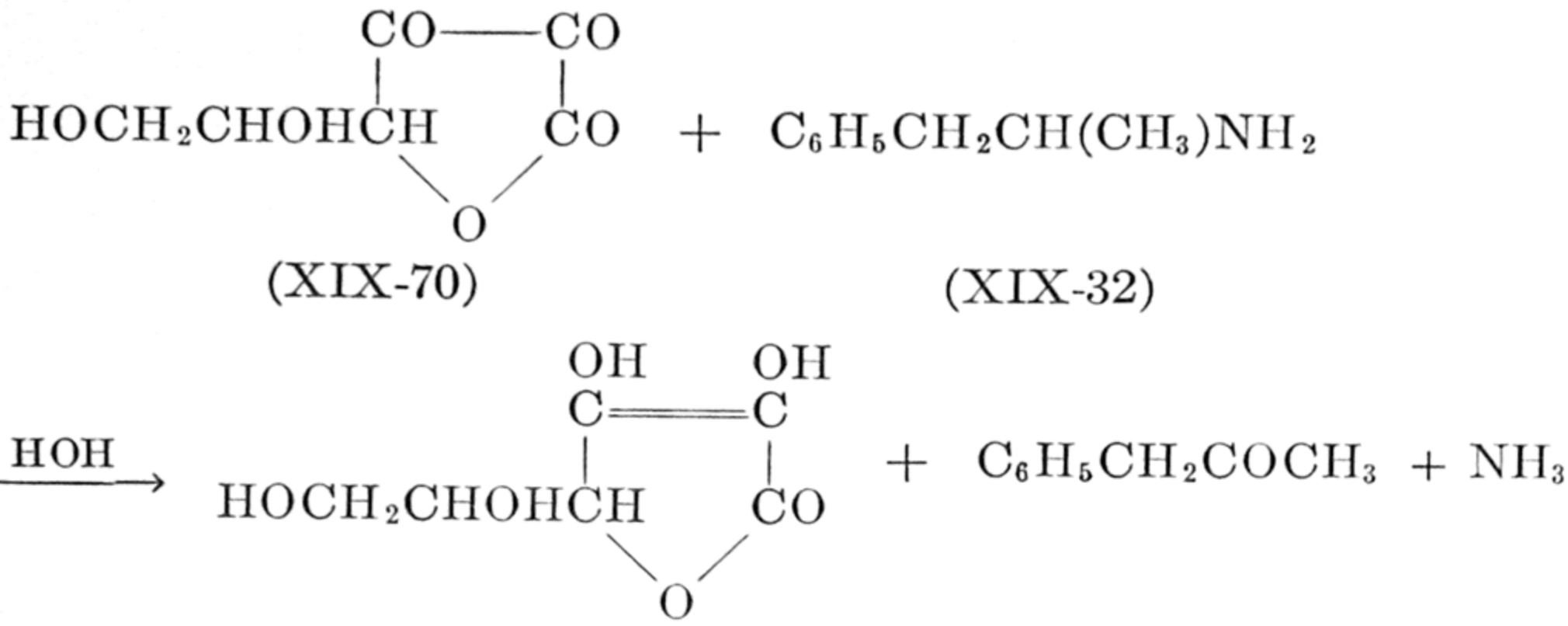
(XIX-68)

The same resistance to deamination by monoamine oxidase exhibited *in vitro* is apparent *in vivo* with secondary carbinamines. Ephedrine, desoxyephedrine ($C_6H_5CH_2CH(CH_3)NHCH_3$) and amphetamine are excreted unchanged slowly in varying amounts over periods of many hours. These refractory (unreactive) amines are deaminated, however, by other biological carriers. When an animal receiving amphetamine is treated with ascorbic acid (XIX-69) less of the drug is excreted unchanged, and more of it is deactivated. The coenzyme responsible for this reaction must be the ascorbic-dehydroascorbic acid (XIX-70) system which has been shown to deaminate both primary and secondary carbinamines.[74]

Since the oxidation-reduction process of this pair of compounds is well understood, we may picture the role of amphetamine as that of an intermediate donor of hydrogen. This has been proved by isolating phenylacetone from the reaction mixture.

The deactivation of Propadrine (XIX-30) and ephedrine (XIX-23) is probably coupled with the fate of the natural pressor hormone, epinephrine. Ephedrine alone, at a dilution of 1×10^{-3}, does not raise the blood pressure, but if a solution 100 times weaker is added to epinephrine a much stronger pressor effect is noted than could be obtained from epinephrine alone. This may perhaps be explained by assuming that ephedrine prevents epinephrine from being destroyed by competing with it for the same detoxicating enzyme system, or that ephedrine stimulates the

[72] Bernheim and Bernheim, *J. Biol. Chem.*, **123,** 317 (1938).
[73] Richter, *Biochem. J.*, **32,** 1763 (1938).
[74] Beyer, *J. Pharmacol. Exptl. Therap.*, **71,** 394 (1941); **76,** 149 (1942).



(XIX-70) (XIX-32)

(XIX-69) (XIX-34)

secretion of the hormone.[75] Since, however, epinephrine is disposed off by a mechanism differing from monoamine oxidase deamination (see below) this explanation needs further proof. If it were true that Propadrine, ephedrine and other secondary carbinamines owe their activity to their inertness toward monoamine oxidase,[76] the absence of all pressor activity of the simple isomer of ephedrine, $C_6H_5CHOHCH(C_2H_5)NH_2$, becomes hard to explain.[77]

A series of substituted N-hexylamines synthesized by Blicke[78] (RNH-n-C_6H_{13}), were tested as pressors, and as potentiators of epinephrine, ephedrine and other sympathomimetic drugs. Many of these compounds potentiate the pressor action of both ephedrine which is not destroyed by amineoxidase, and of phenethylamine which is rapidly destroyed by the same enzyme.[79] If the activity of ephedrine is caused by its inhibition of the enzyme, it could barely be potentiated by other adrenergic amines which are supposed to act by the same mechanism. It must be assumed, therefore, that phenethylamine and ephedrine owe their activity to their ability to inactivate divergent enzyme systems. It must not be overlooked, however, that the same potentiating derivative of hexylamine might react with different enzymes, but the known specificity of enzymes speaks against this interpretation. It has also been considered possible that the effector cell (its enzymes combining with the potentiator?) becomes sensitized by the reagents. Obviously, the whole question of con-

[75] Gaddum, *Brit. Med. J.*, **1,** 713 (1938). Gaddum and Kwiatkowsky, *J. Physiol.*, **94,** 87 (1938).
[76] Beyer, *J. Pharmacol. Exptl. Therap.*, **71,** 151 (1941).
[77] Hartung, Munch, Deckert, and Crossley, *J. Am. Chem. Soc.*, **52,** 3317 (1930).
[78] Blicke and Monroe, *J. Am. Chem. Soc.*, **61,** 91 (1939). Blicke and Zienty, *ibid.*, **61,** 771 (1939).
[79] Lewis, *Proc. Soc. Exptl. Biol. Med.*, **61,** 343 (1946).

nection of activity and enzymatic deamination has not yet received a final answer.

The practical conclusion to be drawn from the resistance of secondary carbinamines to enzymatic deactivation is the possibility that they owe their long duration of action to their biochemical inertness. This condition has both advantages and disadvantages. On the positive side, many members of this series have oral activity and a desirably prolonged therapeutic effect. The main disadvantage lies in the fact that the slow rate of enzymatic destruction permits accumulation of the drugs in the tissues and gives rise to toxic manifestations which may prevent their application in medicine.

3. Detoxication of Catechol-Type Pressor Amines

Epinephrine is detoxicated *in vivo* so rapidly that the relatively slow-acting monoamine oxidase cannot be the only enzyme causing its destruction. Cobefrine and Epinine (XIX-47) behave, on the whole, in a similar manner. It would be convenient to assume that these 3,4-*ortho*-diphenolic drugs are oxidized to *o*-quinoid compounds, and this is actually the case *in vitro* (see below). But one of the enzymes needed to bring about this oxidation, a phenolase (mushroom catecholase), is not found in the tissues of mammals, and is thus ruled out.

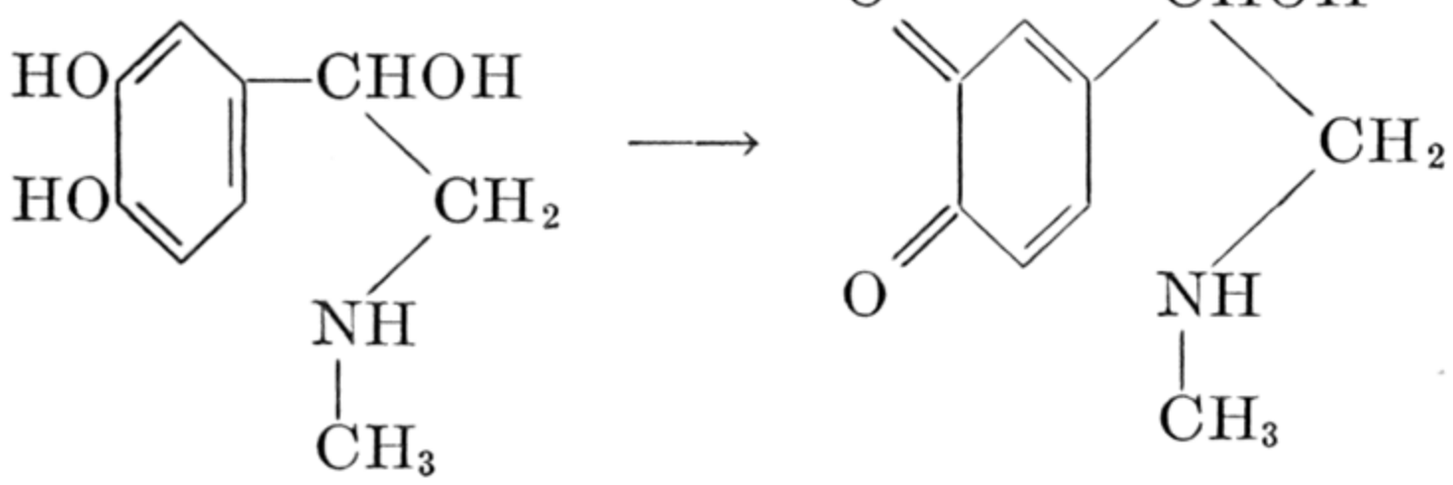
The other enzyme system which destroys epinephrine *in vitro* owes its oxidative ability mainly to cytochrome. However, cytochrome does not oxidize epinephrine *in vivo* in the same manner.[80] While none of the enzyme systems studied so far seem to be the cause of the inactivation of *ortho*-biphenolic pressor amines *in vivo*, the metabolic products of these drugs isolated from the urine have given a clue as to their fate. Richter[81] isolated sulfuric acid conjugates (sulfate esters) of these phenolic compounds, which exist apparently as zwitterions, e.g., $^{-}OSO_2OC_6H_3(OH)CHOHCH_2NH_2^{+}CH_3$. There is much evidence of purely biochemical nature for the fact that conjugation precedes oxidation, and the *in vivo* disposition of epinephrine, Cobefrine and Epinine by this mode of esterification, perhaps under the influence of the enzyme sulfosynthase, is now generally accepted. Whether the natural hormone epinephrine is inactivated by the same mechanism is still uncertain.[82] The *in vitro* fate of epinephrine and its *o*-biphenolic analogs under the influence of catechol oxidase re-

[80] Keilin and Mann, *Proc. Roy. Soc.* (London), **B125,** 187 (1938).

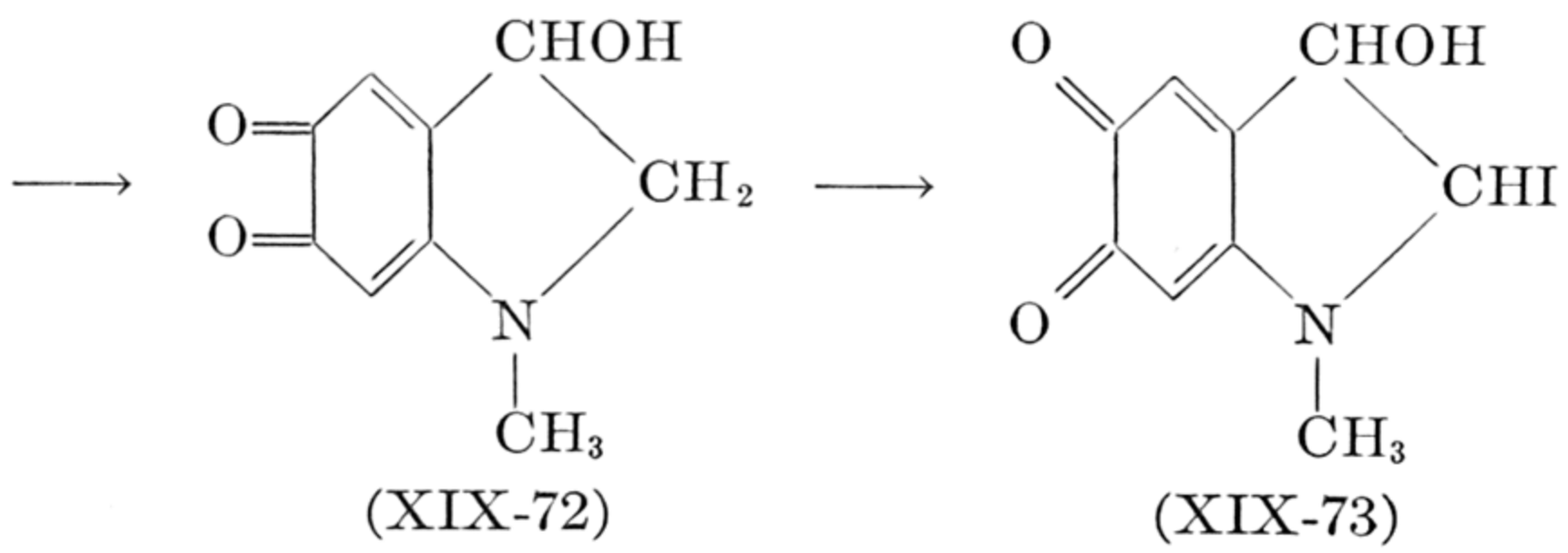
[81] Richter, *J. Physiol.*, **98,** 361 (1940). Richter and MacIntosh, *Am. J. Physiol.*, **135,** 1 (1941).

[82] Hartung, *Ann. Rev. Biochem.*, **15,** pp. 610–611 (1946). Beyer, *J. Pharmacol. Exptl. Therap.*, **79,** 85 (1943); *Am. J. Physiol.*, **144,** 321 (1945); *Physiol. Revs.*, **26,** 169 (1946).

sembles that observed with inorganic oxidizing agents. Epinephrine first loses the two hydrogen atoms in the phenolic hydroxyls, and the *o*-quinone derivative (XIX-71) from this reaction cyclizes to the indole derivative, adrenochrome (XIX-72). The latter is quite unstable and polymerizes to melanin pigments, but can be fixed by iodination to iodoadrenochrome (XIX-73).



(XIX-1) (XIX-71)



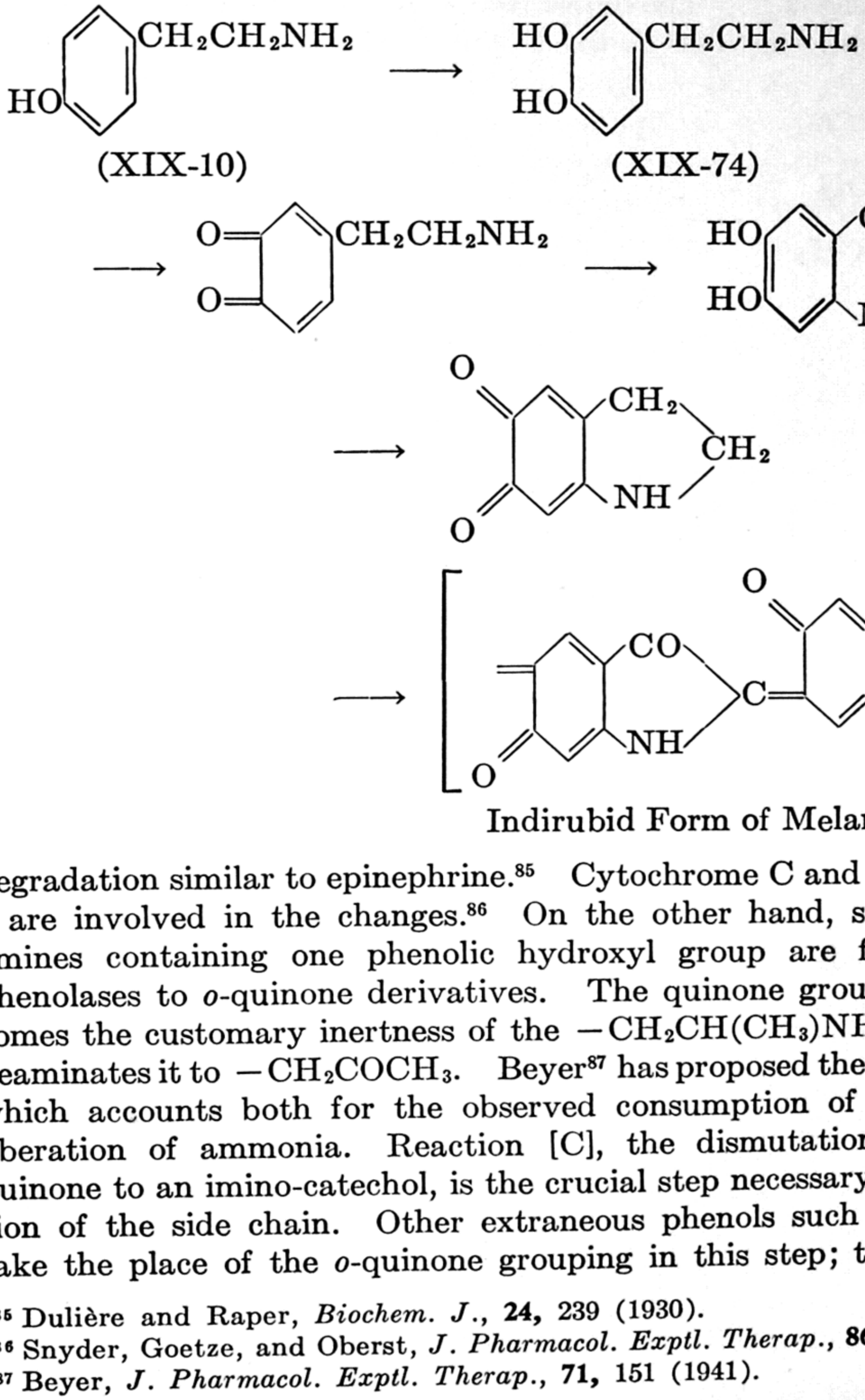
(XIX-72) (XIX-73)

Adrenochrome acts as a carrier in the dehydrogenation of (−)-malic or (+)-lactic acid in the presence of coenzyme I. If adrenochrome is replaced by (+) or (−) epinephrine, Epinine, Cobefrine or N-methylcobefrine, a lag in catalytic activation is observed before these substrates are oxidized to adrenochrome pigments. Succinic acid is dehydrogenated by these combinations in the same way, and glyceraldehyde is probably oxidized by epinephrine as a specific carrier. The pressor amines of this group, or the adrenochrome pigments derived from them, may take the place of flavins in these biological oxidation chains.

Under special conditions,[83] the deep adrenochrome color, accompanied by the loss of hypertensive properties of the oxidized epinephrine solution, will suddenly disappear, and the now pale-yellow solution *decreases* the blood pressure. Further oxidation causes precipitation of polymeric melanin. The nature of the unstable intermediate depressor agent is not understood; the compound has been named adrenoxine.[84]

[83] Bacq, *Compt. rend. soc. biol.*, **127,** 341 (1938).
[84] Heirman, *Compt. rend. soc. biol.*, **126,** 1264 (1937); **127,** 343, 345, 825, 827 (1938).
Bacq, *ibid.*, **129,** 1268 (1937).

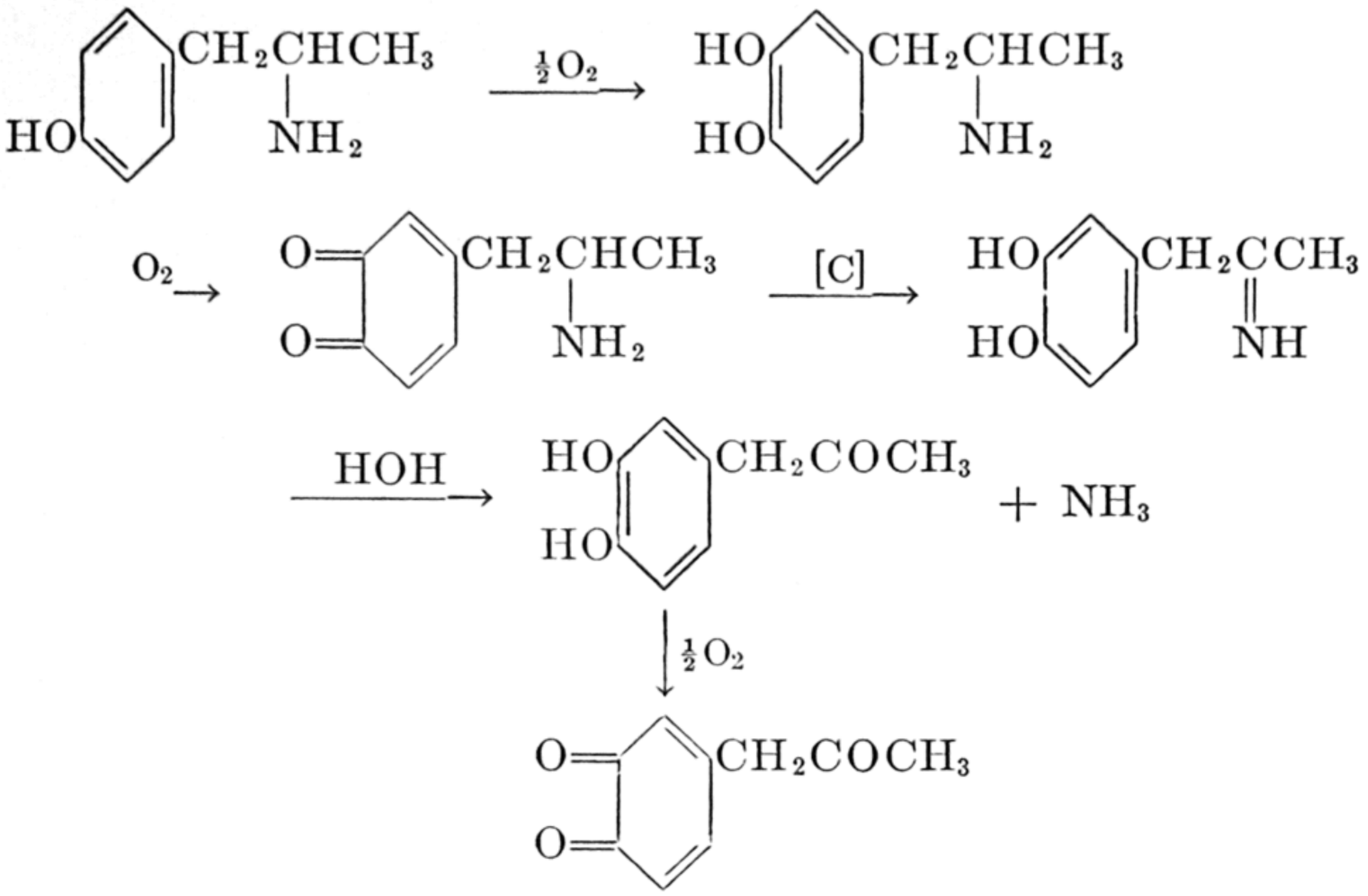
Monophenolic phenethylamine derivatives, such as tyramine, are oxidized by the enzyme tyrosinase *o*- to the existing phenolic hydroxyl group. The biphenolic intermediate (XIX-74) then suffers an oxidative



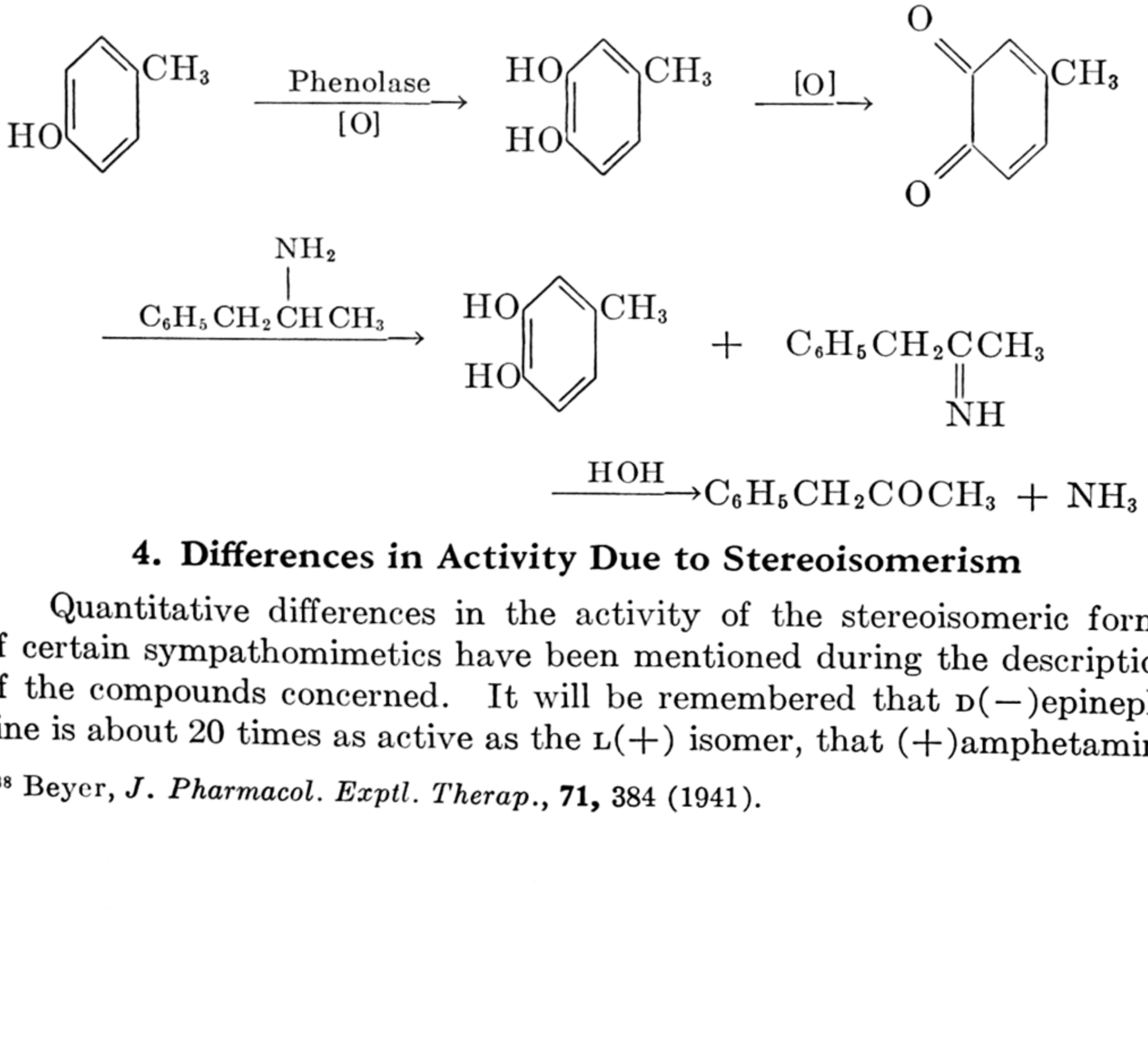
Indirubid Form of Melanin Pigment

degradation similar to epinephrine.[85] Cytochrome C and codehydrogenase I are involved in the changes.[86] On the other hand, secondary carbinamines containing one phenolic hydroxyl group are first oxidized by phenolases to *o*-quinone derivatives. The quinone group, in turn, overcomes the customary inertness of the $-CH_2CH(CH_3)NH_2$ side chain and deaminates it to $-CH_2COCH_3$. Beyer[87] has proposed the following scheme which accounts both for the observed consumption of oxygen and the liberation of ammonia. Reaction [C], the dismutation of the amino-quinone to an imino-catechol, is the crucial step necessary in the deamination of the side chain. Other extraneous phenols such as *p*-cresol may take the place of the *o*-quinone grouping in this step; they are oxidized

[85] Dulière and Raper, *Biochem. J.*, **24,** 239 (1930).
[86] Snyder, Goetze, and Oberst, *J. Pharmacol. Exptl. Therap.*, **86,** 145 (1946).
[87] Beyer, *J. Pharmacol. Exptl. Therap.*, **71,** 151 (1941).



to quinones by the enzyme, and in turn oxidize the secondary carbinamine.[88]



4. Differences in Activity Due to Stereoisomerism

Quantitative differences in the activity of the stereoisomeric forms of certain sympathomimetics have been mentioned during the description of the compounds concerned. It will be remembered that D(−)epinephrine is about 20 times as active as the L(+) isomer, that (+)amphetamine

[88] Beyer, *J. Pharmacol. Exptl. Therap.*, **71,** 384 (1941).

is a more powerful central stimulant than (−) amphetamine, and that D(−)ephedrine and L(+)pseudoephedrine are more active than their respective isomers. These differences are explainable on the basis of the stereochemical specificity of the cell protoplasm. The "receptor" substance, presumably unchanged sterically through millions of generations of cells, fits the shape of the molecule of a drug to its own when it comes in contact with the foreign chemical. We do not need to think of the interaction of drug and plasma constituent as a chemical alteration of both participants, but often only as the mutual fitting of molecular cavities, corners and other space relations. A chemically extremely similar drug, such as the optical isomer of an active compound, will be able to enter all the nooks and crannies of the influenceable plasma molecule except those into which its configuration will not fit. A greater number of the same type receptor molecules will have to be occupied, that is, a higher number of the less suitable drug molecules will be used up to produce the same effect as the sterically fitting, more efficient isomer.

A new difficulty is introduced when stereoisomeric forms of a drug produce not only quantitatively but qualitatively different physiological symptoms. It is then no longer easy to see how one and the same protoplasmic reagent could respond to the sterically different shapes of the same drug in a manner which produces far-reaching different effects. It may be, of course, that functional groups unoccupied by a sterically ill-fitting isomer become involved in reactions with entirely unrelated reagents and thus give rise to new symptoms. But the possibility cannot be disregarded that stereoisomers react with two sterically or otherwise differentiated substrates, leaving the unreacted plasma reagent free to cause, by irrelevant other chemical transformations, a new set of symptoms.

Whichever of these explanations is accepted, profound qualitative differences in the effects of stereoisomers have become known. In the field of sympathomimetics, the pharmacological effects of the optical isomers of Synephrine (4-$HOC_6H_4CHOHCH_2NHCH_3$) may serve as suitable examples.[89] The (+) isomer causes vasodilation in doses of 10 mg., whereas the (−) isomer causes vasoconstriction in very small doses (0.5 − 2.0 mg.). Doses of the racemic mixture up to 50 mg. do not constrict peripheral blood vessels, and since this 50 mg. consists of equal parts (25 mg.) of the two isomers, it is obvious that the vasodilating (+) form can overcome completely the inherently much more powerful vasoconstrictor action of its optical isomer.

The qualitative and therapeutically important variations between (+) and (−) amphetamine have been mentioned but the astonishing dif-

[89] Tainter, *J. Pharmacol. Exptl. Therap.*, **40,** 43 (1930). Tainter and Seidenfeld, *ibid.*, **40,** 23 (1930).

ferences between the salts of stereoisomeric acids with (−) amphetamine defy, at present, explanation. The *l*-mandelate of the *l*-base is approximately 47% more active than the *d*-mandelate; the physiologically active base is sterically the same in both salts, and neither of the forms of mandelic acid is known to exert a noticeable effect on the blood pressure.[90] Hartung[91] has reasoned that the modification of the activity of the base brought about by a supposedly nonparticipating acid may mirror similar modifications of an active drug by different tissue constituents of yet unknown nature.

How chemical changes at asymmetric centers may modify the quality of pharmacodynamic properties has been shown in the case of the drug Cobefrine ($3,4\text{-}(HO)_2C_6H_3\overset{*}{C}HOH\overset{*}{C}H(CH_3)NH_2$). Two of the four possible optical isomers have been studied, one *d*- and one *l*- form.[92]

The *l*- form has up to 200 times the pressor action of the *d*- form and is qualitatively similar to epinephrine. The *d*- form possesses centrally stimulating action. Reduction of the alcoholic hydroxyl of either isomer leads to 1-(3,4-dihydroxyphenyl)-2-aminopropane [$(HO)_2C_6H_3CH_2\overset{*}{C}H(CH_3)NH_2$] which retains only one asymmetric carbon atom; the reduction product from either source behaves similar to ephedrine, and has lost its epinephrine-like qualities.

VI. CHEMICAL STRUCTURE AND ADRENERGIC ACTION

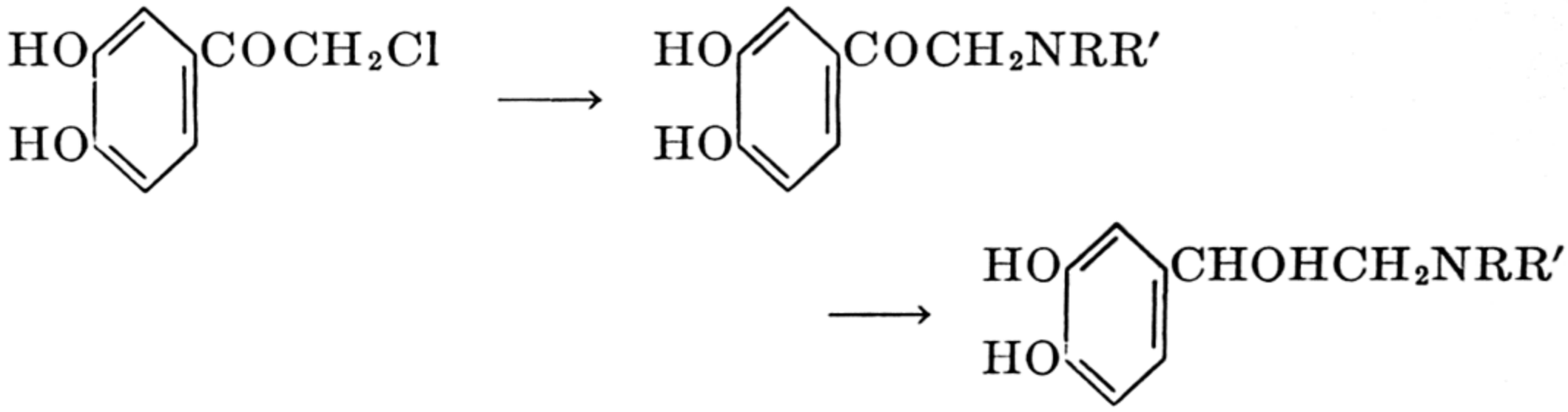
1. β-Arylethylamine Derivatives

The study of the biochemical behavior of sympathomimetic amines has done more for the theoretical background of medicinal chemistry than purely statistical deductions of relation of structure and properties drawn from endless tables of synthetic variations. Nevertheless, such deductions can and must be drawn even in this field since the enzymatic deactivation of theses amines has not yet answered all questions. Why does Adrenalin principally raise the blood pressure while its simple homolog, Isuprel, lowers it in therapeutic doses? Why does 1-phenyl-2-aminobutane have so much less activity than its lower homolog, amphetamine? How about quantitative, and expecially the qualitative differences of stereoisomers? Such fine points cannot yet be explained by differences in the rate of reactions of the compounds concerned. A survey of the relations between structure and activity is therefore of value, even though

[90] Swanson, Scott, Lee, and Chen, *J. Pharmacol. Exptl. Therap.*, **79,** 329 (1943).
[91] Hartung, *Ind. Eng. Chem.*, **37,** 126 (1945).
[92] Schaumann, *Arch. exp. Path.*, **181,** 137 (1936).

all attempts to arrive at some empirical conclusion must remain speculative at this time.[93]

When the synthesis of epinephrine had been performed, Stolz[16] had a suitable intermediate at his command which permitted the preparation of variants of the hormone structure. From this intermediate, chloroacetyl catechol, $3,4\text{-}(HO)_2C_6H_3COCH_2Cl$, a number of amino ketones and the corresponding amino alcohols were readily available. Their pharmaco-



logical study by Loewi and Meyer,[94] and that of a similar series by Dakin[95] revealed that the amino alcohols had, on the whole, a greater degree of "Adrenalin-like" action than the amino ketones, provided the amino radicals were not too complicated.

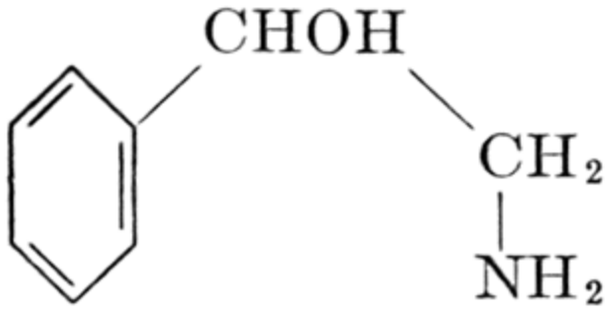
As in so many other pharmacological studies, the evaluation of different chemicals on the basis of a multiple effect such as that of Adrenalin has remained difficult. Adrenalin not only raises the blood pressure by a variety of convergent individual actions, but it also inhibits the tone and rhythm of the muscular walls of the mammalian intestine and of the urinary bladder of the cat. Furthermore, it stimulates the pregnant uterus of this animal, and inhibits its movements in the absence of pregnancy, or in the virgin state. These statements from the classical article by Barger and Dale[9] presage the dilemma of a large chemical screening program in this field. There are many amines which are superior to Adrenalin in one or another of these activities but while their ultimate usefulness may be determined by just these special and selective preferences of effector organs, a readily measurable property common to almost all of them is a must for preliminary screening. This property is the rise in the blood pressure, or its occasional lowering, produced by this class of compounds. With all its shortcomings, the evaluation of sympathomimetic amines as pressor drugs has become their main point of comparison. For a finer gradation of effects, a more comprehensive study with special attention to the effects on the uterus should be useful for each compound. Such a

[93] Hartung, *Chem. Revs.*, **9,** 389 (1931).
[94] Loewi and Meyer, *Arch. exp. Pathol. Pharmacol.*, **53,** 213 (1905).
[95] Dakin, *Proc. Roy. Soc.*, **B76,** 491 (1905).

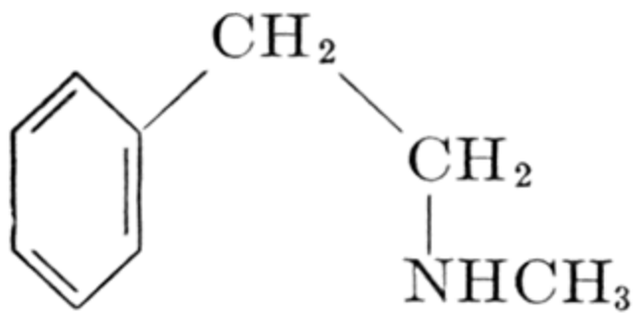
procedure has made it possible to recognize, at an early date, that the closer the approach to the structure of Adrenalin, the more can a drug be expected to duplicate all the various actions of the hormone. As Barger and Dale put it, "approximating to Adrenalin in structure is, on the whole, attended with increasing intensity of sympathomimetic activity, and with increasing specificity of action".

There was not much use in looking for sympathomimetic activity in aniline; neither did benzylamine have any promising properties, nor did 1-amino-1-phenylethane ($C_6H_5CH(CH_3)NH_2$) in which only one carbon atom separates the aromatic nucleus from the amino group. Phenethylamine showed high but brief activity, about 100 times that of epinephrine. In 3-phenylpropylamine a decline was noted which continued (as shown by later investigators) as the distance between the ring and the nitrogen function was heightened. The optimum conditions were thus reached in the outline structure Ar-C-C-N. All important and most active modern adrenergic drugs contain this skeleton.

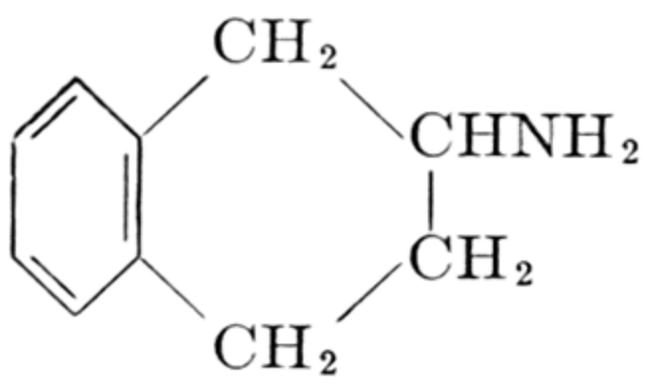
Even considerable chemical manipulation of the phenethyl group does not produce decisive deviations in activity. Introduction of an alcohol function (XIX-75), monomethylation of the amino group (XIX-76), or even incorporation of the side chain in a ring in 2-amino-1,2,3,4-tetrahydronaphthalene (XIX-77) does not affect activity on peripheral blood pressure. However, other similar cyclic amines in which the phen-



(XIX-75)

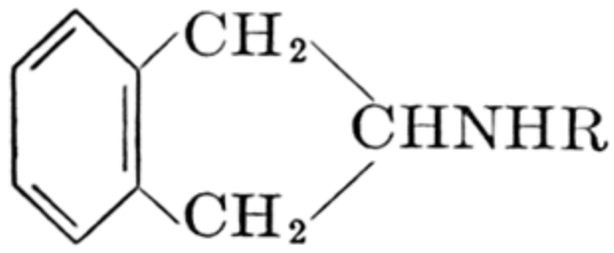


(XIX-76)

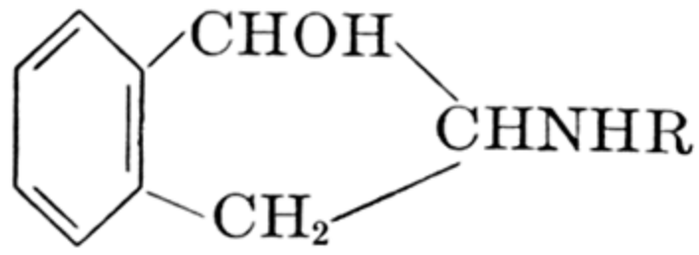


(XIX-77)

ethyl structure has been preserved do not possess much activity. The N-alkyl derivatives of aminoindane (XIX-78) and indanolamine (XIX-79) are a case in point, but they are interesting because of their bronchodilator action.[96] If the carbon atoms of the side chain become part of an



(XIX-78)

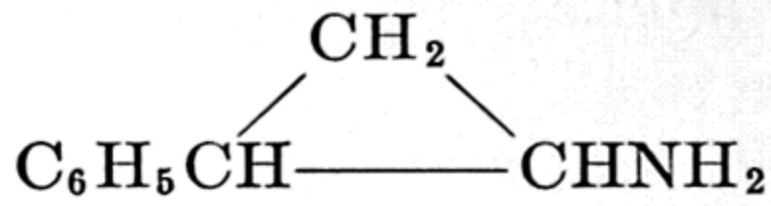


(XIX-79)

alicyclic ring, the pressor as well as the effect on the central nervous system appears to be lowered.

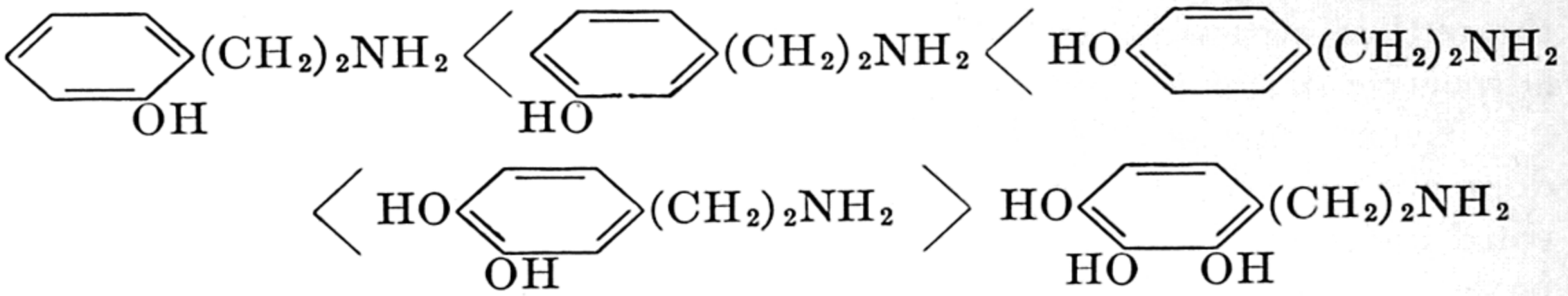
[96] Levin, Graham, and Kolloff, *J. Org. Chem.*, **9,** 380 (1944).

2-Phenylcyclopropylamine (XIX-80)[96a] has only 0.001 to 0.017 the pressor action of epinephrine, and only about one seventh the centrally excitant effect of Benzedrine. Its MLD is 50-60 mg./kg. (in rats, intraperitoneally).[97]



(XIX-80)

Substitution of phenethylamine by a phenolic hydroxyl group leads to compounds of increasing strength as the phenolic group is moved from the *ortho* to the *meta* and to the *para* position. Two phenolic hydroxyls, especially in the catechol structure, produce even more powerful compounds, while analogous derivatives with three phenolic hydroxyl groups exhibit less pressor activity than the catechol types. The action of these



compounds is intensified, in general, by the introduction of an alcoholic hydroxyl group at the carbon atom of the benzyl position; the phenolic β-phenylethanolamines are strong pressor substances.

Extensive systematic variations of the amino group have not made possible overall conclusions about the influence of N-alkylation on pressor activity. On the whole, N-methyl compounds appear less active than the corresponding primary amines but this generalization has many exceptions; 3,4-dihydroxyphenethylamine is four times less active than its N-methyl derivative. In many cases the decrease in pressor activity is accompanied by a rise in toxicity of the methylamine derivative. This holds even more for dialkylated compounds; tertiary amines of this series lose activity and gain toxicity as the size of the alkyl groups is increased. Many are no longer pressors but possess analgetic properties (see Section VIII).

Monoalkylation of the primary amino nitrogen is difficult to evaluate in generalized terms; both increases and decreases of activity have been observed after monomethylation. Larger alkyl groups may again have varied effects. Thus, replacement of the N-methyl group in epinephrine by N-isopropyl in Isuprel causes a change from vasopressor to depressor

[96a] Burger and Yost, *J. Am. Chem. Soc.*, **70,** 2198 (1948).
[97] Fellows, private communication.

type action, and a simultaneous increase of bronchodilator activity. Dialkylation results usually in a decrease or loss of activity. The quaternary salts derived from adrenergic amines conform to the general rule that quaternization causes curariform activity (Chapter XXII); however, hordenine methiodide ($4\text{-}HOC_6H_4CH_2CH_2\overset{+}{N}(CH_3)_3\overset{-}{I}$) acts like nicotine rather than curare.

A radical change in the character of the side chain abolishes adrenergic activity. The α-amino acids of the phenylalanine type ($C_6H_5CH_2CH(COOH)NH_2$) from which the naturally occurring active bases may be derived are without action. The literature does not report the effect on the blood pressure of esters or amides of amino acids in which the essentially basic properties of the sympathomimetic side chain have been restored.

Among the most interesting comparisons of substitutents of the side chain are those between various alkyl groups, and between methyl and hydroxyl. The effect of the methyl group on the β-carbon atom in stabilizing the molecule against enzymatic attack has been described. As may be expected, removal of the methyl group to the α-carbon atom ($C_6H_5CH(CH_3)CH_2NH_2$) makes for less biochemical interference, and the duration of the effect of this compound is shorter than that of the isomeric amphetamine ($C_6H_5CH_2CH(CH_3)NH_2$). As the size of the alkyl group in the β-position is increased, the compounds become more refractory to deamination, and are therefore retained longer in the system. Both their toxicity and vasopressor activity rise.

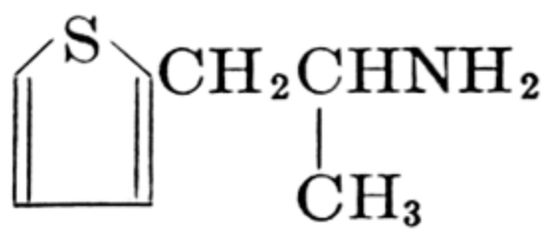
The hydroxyl group has about the same weight (17) as methyl (15); they may be expected to have approximately the same size, and have been regarded as isosteric.[98] It is doubtful whether this view could be defended since the term isosterism covers similarities in reactivity as well as spatial bulk. However, a definite analogy is found in the pharmacological properties of 2-phenyl-1-aminopropane ($C_6H_5CH(CH_3)CH_2NH_2$) and phenylethanolamine ($C_6H_5CHOHCH_2NH_2$); they both are as pressors equal to epinephrine, and have about the same toxicity. The N-methyl derivatives of these two compounds, $C_6H_5CH(CH_3)CH_2NHCH_3$ and $C_6H_5CHOHCH_2NHCH_3$, are both about equally much less toxic than N-methylphenethylamine, $C_6H_5(CH_2)_2NHCH_3$. A further analogy can be drawn between the homologous β-phenylpropanolamine ($C_6H_5CHOHCH(CH_3)NH_2$) which shares with the "isosteric" 2-amino-3-phenylbutane ($C_6H_5CH(CH_3)CH(CH_3)NH_2$) a lack of stimulatory properties.

Observations parallelling those concerning alkyl substitution in the side chain have been made with alkyl groups in the aromatic nucleus.

[98] Hartung, *Chem. Revs.*, **37,** 126 (1945).

Again, methylation lowers activity and increases toxicity, expecially in derivatives containing an ethanolamine side chain. Larger aliphatic nuclear substituents ultimately abolish activity completely, while a benzyl group may produce depressors.

Derivatives of cyclohexane containing β-ethylamine or β-isopropylamine side chains have vasopressor properties. This shows that the fundamental structure, Ar-C-C-N-, is amenable to considerable variations. It is not surprising, that the benzene ring can be replaced by the isosteric thiophene nucleus without appreciable loss of activity.[99] The isostere of amphetamine, β-(2-thienyl) isopropylamine (XIX-81), is highly active in dogs on intravenous injection.[100] Nevertheless, none of these nuclear



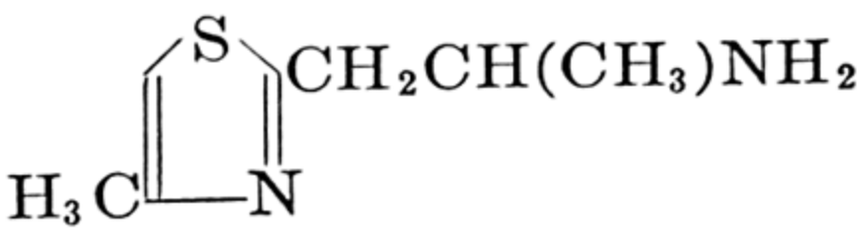
(XIX-81)

alterations have produced a drug which could rival the best of the substituted phenethylamine derivatives in activity and therapeutic index.

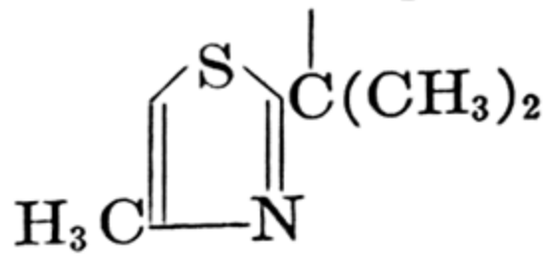
2-(α-Pyridyl) isopropylamines substituted by methyl or ethyl in positions 5 or 6, are principally analgetics. These compounds are prepared from the corresponding picolyl lithium derivatives and acetonitrile, and subsequent application of the Leuckart reaction to the respective pyridylacetone.[101]

$$\text{RPy-2-CH}_2\text{Li} \xrightarrow[2.\ \text{HOH}]{1.\ \text{CH}_3\text{CN}} \text{RPy-2-CH}_2\text{COCH}_3 \longrightarrow \text{RPy-2-CH}_2\text{CH(CH}_3\text{)NH}_2$$

1-(4-Methyl-2-thiazolyl)-2-aminopropane (XIX-82) and its N-methyl derivative had a certain stimulating effect on the cerebrum, but the action was weaker than that of Benzedrine. The toxicity of these compounds was also lower than that of the reference drug. The isomer (XIX-83) had a sedative rather than an analeptic effect.[102]



(XIX-82)



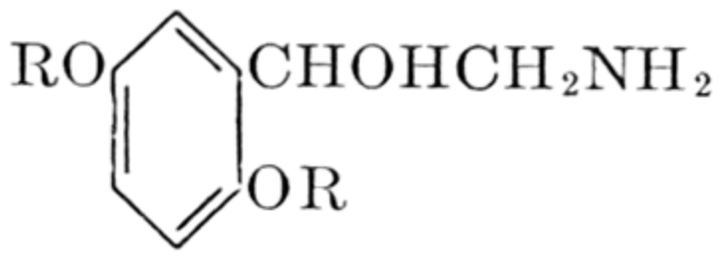
(XIX-83)

[99] Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64,** 477 (1942).
[100] Warren, Marsch, Thompson, Shelton, and Becker, *J. Pharmacol. Exptl. Therap.*, **79,** 187 (1943). Alles and Feigen, *ibid.*, **72,** 265 (1941).
[101] Burger and Ullyot, *J. Org. Chem.*, **12,** 342 (1947).
[102] Ekstrand, *Acta Chim. Scand.*, **2,** 727 (1948).

p-Chlorophenethylamine is considerably more active than phenethylamine, but a similar relation does not prevail for the pair *p*-chlorophenylpropanolamine (*p*-$ClC_6H_4CHOHCH(CH_3)NH_2$) and phenylpropanolamine. The former is three times more toxic than its parent compound, and only one fourth as active. Introduction of fluorine into nuclear positions *o*-, *m*-, or *p*- to the side chain again leads to increased toxicity; the pressor properties of such compounds are irregular.

The data for monophenolic phenethylamines and phenylethanolamines recorded by Barger and Dale have painted only a part of the picture of nuclear monohydroxy substitution, because no derivatives with branched side chains had been included in their study. The more recently prepared pairs of compounds are mainly *m*- and *p*- hydroxy derivatives since ortho substitution has not led to particularly promising compounds. The *m*-substituted compounds are on the whole more effective pharmacologically, both in regard to pressor activity and, unfortunately, general toxicity. The *p*-isomers are less toxic than the non-phenolic parent amino alcohol but have a greater pressor activity; this does not, however, match that of the *m*- isomer. A significant difference between the isomers of each pair lies also in their respective type of action. The *p*-isomers simulate, on the whole, the effect of postganglionic sympathetic nerve fibers on muscles while the *m*- isomers show a more generalized effect, approaching that of the more disperse epinephrine. This may explain their greater total activity.

Powerful pressor activity is exhibited by dialkoxy derivatives of type (XIX-84).[103]



(XIX-84)

Amino substitution of the aromatic ring has been studied on a limited scale. *p*-Aminoephedrine is about twice as active, and half as toxic as ephedrine and thus resembles *p*-hydroxyephedrine pharmacologically.[104] β-(*p*-Aminophenyl)-N,N-dimethylethylamine (4-$H_2NC_6H_4CH_2CH_2N(CH_3)_2$) raises the blood pressure by a mechanism similar to that of nicotine; it is ten times more active than its parent compound without the nuclear amino group ($C_6H_5CH_2CH_2N(CH_3)_2$).[105]

The trend towards greatest pressor activity is thus noticeable both in *meta* and *para* substituted derivatives, and highest potency is attained

[103] Buck, Baltzly and Ide, *J. Am. Chem. Soc.*, **62,** 164 (1940); **68,** 591 (1946); **70,** 1084 (1948).

[104] Tainter, *Arch. intern. pharmacodynamie*, **46,** 192 (1933)

[105] Bovet and Benoit, *Compt. rend. soc. biol.*, **136,** 328 (1942).

in compounds which combine both types of nuclear substitution, that is, in catechol derivatives having the two hydroxyls in positions 3 and 4. Epinephrine, Cobefrine, and Epinine are examples for this rule. That the opposite effect on blood pressure may also occur in this series is attested by Butanefrine and Isuprel which are principally vasodepressors; however, Isuprel increases cardiac rate much more effectively than epinephrine.

Nuclear position isomers of the therapeutically valuable 3,4-dihydroxy compounds which have the two phenolic groups in other relative nuclear positions have not been studied adequately. Etherification of the phenolic hydroxyls leads to alkoxyphenethylamines and alkoxyphenylethanolamines. The methoxyl derivatives have been investigated carefully, but beyond the uncertain statement that most of them are less active and more toxic than the corresponding phenolic derivatives, no valid trend of relations of their structure and pharmacological activity has been elaborated.[106]

2. Aliphatic Pressor Amines

Because isoamylamine is formed from leucine by putrefaction and shows definite pressor properties, Barger and Dale[9] included a few aliphatic amines in their original investigation.

Of the normal primary aliphatic amines from one to fifteen carbon atoms, *n*-hexylamine was the most active pressor amine. The higher members of the series became increasingly toxic and depressant, apparently in relation to the increasing preponderance of the "narcotic alkyl" over the "excitant amino" group. Also, the low solubility of the higher members of the series made testing difficult.

Isoamylamine, $(CH_3)_2CHCH_2CH_2NH_2$, was found to be less active than the normal isomer; likewise, secondary aliphatic amines were weaker pressors than the primary analogs.

Introduction of a second amino group as it is done in pentamethylene diamine (cadaverine) leads to a virtual reversal of activity; cadaverine is a vasodepressor. It appears that no valid comparison between the pressor activity of aliphatic diamines, and that of the catechol type diamines mentioned above, can be drawn. A comparison of their bronchodilator action may lead to more satisfactory conclusions. Whatever the pharmacological properties of aliphatic amines, these compounds were not considered to be of practical value as pressor substances by earlier workers.[107]

[106] Graham, Cartland, and Woodruff, *Ind. Eng. Chem.*, **37,** 149 (1945). Hauschild, *Arch. exptl. Pathol. Pharmakol.*, **195,** 647 (1940).

[107] cf. Dunker and Hartung, *J. Am. Pharm. Assoc.*, **30,** 619 (1941).

A recent reinvestigation of aminoalkanes had as its aim to determine the influence of the location of the amino group along the carbon chain, and also the effect of side chains on pressor action.[108] Conditions for optimal activity were found in compounds with 7 to 8 carbon atoms which carry the amino group in the 2-position. The activities of some of these derivatives in the pithed cat, i.e., in animals in which the medulla had been severed near the base of the skull in order to eliminate central nervous system effects on the blood pressure, are listed in Table III. They are expressed as epinephrine equivalents, that is, the milligrams of epinephrine which would produce the same pressor effect as 1 mg. of the amine.

TABLE III. PRESSOR ACTIVITY OF ALIPHATIC AMINES[108]

Sulfate of	Epinephrine Equivalent
Controls: Ephedrine	0.00676
Amphetamine	0.0045
$H_2N(CH_2)_5CH_3$	0.003
$CH_3CH(NH_2)(CH_2)_3CH_3$	0.003
$CH_3CH(NH_2)CH_2CH(CH_3)CH_3$	0.001
$H_2N(CH_2)_6CH_3$	0.00087
$CH_3CH(NH_2)(CH_2)_4CH_3$ (Tuamine)	0.0037
$CH_3CH_2CH(NH_2)(CH_2)_3CH_3$	0.001
$CH_3(CH_2)_2CH(NH_2)(CH_2)_2CH_3$	0.0000
$CH_3CH(NH_2)CH(CH_3)(CH_2)_2CH_3$	0.00125
$CH_3CH(NH_2)(CH_2)_2CH(CH_3)CH_3$	0.002
$CH_3CH(NH_2)CH_2CH(CH_3)CH_2CH_3$	0.005
$H_2N(CH_2)_7CH_3$	0.0000
$CH_3CH(NH_2)(CH_2)_5CH_3$	0.0015
$CH_3CH_2CH(NH_2)(CH_2)_4CH_3$	0.00075
$CH_3CH(NH_2)CH(CH_3)(CH_2)_3CH_3$	0.001
$CH_3CH(NH_2)CH_2CH(CH_3)(CH_2)_2CH_3$	0.0037
$CH_3CH(NH_2)(CH_2)_2CH(CH_3)CH_2CH_3$	0.002
$CH_3CH(NH_2)(CH_2)_3CH(CH_3)CH_3$	0.0033
$CH_3CH(NH_2)CH(CH_3)(CH_2)_2CH(CH_3)CH_3$	0.0015

This comparison demonstrates that branching is in many cases actually necessary for maximum activity. This is borne out for the most active compounds of the series, 2-amino-4-methylhexane, and 2-amino-4-methylheptane.

Other aliphatic amines which have been carried beyond the early stages of experimental study are 2-methylamino-6-methylheptene-5 (Octin, $CH_3C(CH_3)=CH(CH_2)_2CH(CH_3)NHCH_3$), and 2-methylaminoheptane (Oenethyl, $CH_3(CH_2)_4CH(CH_3)NHCH_3$).

[108] Rohrmann and Shonle, *J. Am. Chem. Soc.*, **66,** 1517 (1944).

Certain aliphatic and alicyclic hexylamines provide further proof that pressor activity does not reside only in aromatic derivatives of alkylamines. N-Methylhexylamine ($C_6H_{13}NHCH_3$) and dihexylamine ($(C_6H_{13})_2NH$) are potent pressors, as is N-(γ-cyclohexylpropyl) hexylamine ($C_6H_{11}(CH_2)_3NHC_6H_{13}$); the latter is more active than the corresponding phenyl derivative, but also much more toxic.

A series of secondary β-cyclopentylethyl-($C_5H_9CH_2CH_2NHR$) and β-cyclohexylethylamines ($C_6H_{11}CH_2CH_2NHR$) have also been shown to have distinct sympathomimetic activity.[109] They elevate blood pressure, increase heart rate, and relax the intestinal muscles and the uterus of the cat. The importance of Benzedrex (β-cyclohexylisopropyl-N-methylamine) as a nasal shrinker without analeptic side effects has been discussed before. Methyl-bis-β-cyclohexylethylamine, $(C_6H_{11})_2CHCH_2NHCH_3$, has been introduced as an antispasmodic under the name of Cyverine. The biochemical destruction of these compounds has been described in Section V.

In another series of cycloalkylethylamine derivatives, 1-cyclopentyl-2-methylaminopropane was singled out as a favorable, orally active vasoconstrictor agent.[110]

VII. DIALKYLAMINO ALKOXY-, ALKYLTHIO-, AND ALKYLAMINO-ARYL DERIVATIVES

The most important sympathomimetics in the wider sense of the definition of this term are to be found in the series of aralkylamines, especially the phenethylamines and their functional derivatives, and these compounds are followed by the less active, but occasionally more selective agents in the aliphatic and alicyclic series described on the preceding pages. In addition to these derivatives, interruption of the carbon-to-carbon bonds by (*a*) ether oxygen, (*b*) thioether sulfur, and (*c*) imino groups has also been studied. These compounds may be represented by the following partial formulas.

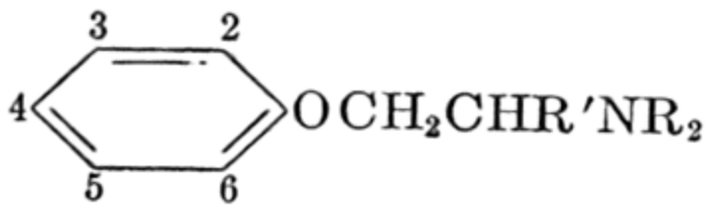
(*a*) Ar-O-C-C-NR_2
(*b*) Ar-S-C-C-NR_2
(*c*) Ar-NH-C-C-NR_2

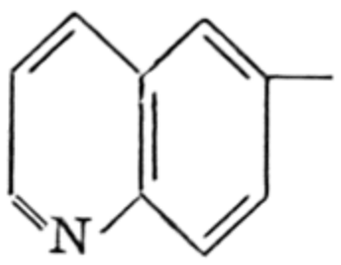
Several of these compounds are sympathomimetic agents. For example, α-phenylthio-β-methylaminoethane ($C_6H_5SCH_2CH_2NHCH_3$) exerts a violent and long-lasting hypertensive action.[111] N-Phenylethylenedi-

[109] Lands, Lewis, and Nash, *J. Pharmacol. Exptl. Therap.*, **83,** 253 (1945).
[110] Chen, *Ann. Otol. Rhinol. Laryngol.*, **57,** 287 (1948).
[111] Benoit and Bovet, *Bull. Soc. Pharmacol.*, **45,** 97 (1938).

amine ($C_6H_5NHCH_2CH_2NH_2$) is also strongly pressor.[112] However, it is not possible to generalize about the type of activity of these compounds. Minor structural changes produce profound qualitative differences, and a considerable specificity of action emerges from the general autonomic properties of the substances. As an example, the structures and pharmacodynamic properties of a few β-phenoxyethylamines are collected in Table IV.

TABLE IV. PHARMACODYNAMIC PROPERTIES OF CERTAIN β-PHENOXYETHYLAMINES[113]



Nuclear Substituents	R′	R	Activity
none	OH	CH_3	Antipyretic
none	H	piperidino	Local Anesthetic
3-OH	H	CH_3	Pressor
none	H	C_2H_5	Sympatholytic
4-NH_2	H	CH_3	Nicotinic
2-Isopropyl-5-methyl	H	C_2H_5	Antihistaminic
2-Allyl-6-OCH_3	H	C_2H_5	Oxytocic
2-phenyl	H	C_2H_5	Antifibrillant
	H	CH_3	Analeptic

VIII. ADRENERGIC AMINES AS ANODYNES

If the recent pharmacological interpretation of algesia (production of pain) as a cholinergic experience, and of analgesia (relief from pain) as an adrenergic process is correct, the pain-obtusing properties of adrenergic amines become more readily understandable. The elevation of the threshold of pain by epinephrine, Synephrine, ephedrine, Paredrinol, desoxyephedrine, and similar compounds has been noted repeatedly,[114] and amphetamine has been observed to potentiate the analgetic action of

[112] Bovet, Lestrange, and Fourneau, *Compt. rend. soc. biol.*, **130,** 1192 (1939).

[113] Bovet and Bovet-Nitti, *Structure et activité Pharmacodynamique des Médicaments du Système Nerveux Végétatif.* Interscience, New York, 1948, p. 231.

[114] Pero, *Giorn. ital. anestesia e analgesia*, **5,** 128 (1939). Puharich and Goetzl, *Permanente Found. Bull.*, **5,** 19 (1947). Ivy, Goetzl, Harris, and Burrell, *Quart. Bull. Northwest. Univ. School Med.*, **18,** 298 (1944).

TABLE V. ANALGETIC DERIVATIVES OF DIPHENYLETHYLAMINE AND DIPHENYLETHANOLAMINE[117]

$C_6H_5CH_2CH(NH_2)CH_3$	$C_6H_5CHOHCH(NH_2)CH_3$
$C_6H_5CH_2CH(NH_2)C_6H_5$	$C_6H_5CHOHCH(NH_2)C_6H_5$
$C_6H_5CH_2CH(NHCH_3)C_6H_5$	4-$HOC_6H_4CHOHCH(NH_2)C_6H_5$
$C_6H_5CH_2CH(NHCH_3)C_6H_4OH(-3)$	$C_6H_5CH_2CH(NHCH_3)C_6H_4OH(-4)$
$C_6H_5CH_2CH(NHCH_3)C_6H_4OC_2H_5(-3)$	$C_6H_5CH_2CH(NHCH_2C_6H_5)C_6H_4OH(-4)$
	3-CH_3O-4-$HOC_6H_3CH_2CH(NH_2)C_6H_5$

TABLE VI.[115] PHENYLALKYLAMINE AND ANALOGOUS DERIVATIVES EXHIBITING MARKED ANALGETIC ACTIVITY IN CATS

Compoun	Dose mg./kg.	
	Effective	Toxic
4-$CH_3C_6H_4CH_2CH(CH_3)NH_2$	10	20+
4-$CH_3OC_6H_4CH_2CH(CH_3)NH_2$	2	6
4-$CH_3OC_6H_4CH_2CH(CH_3)NHCH_2C_6H_5$	25	35
4-$CH_3OC_6H_4CH_2CH(CH_3)$NH-isoPr	20	50
4-$HOC_6H_4CH_2CH(CH_3)NH_2$	2	30
d-4-$HOC_6H_4CH_2CH(CH_3)NH_2$	2	20
4-$C_6H_5CH_2COOC_6H_4CH_2CH(CH_3)NH_2$	20	30
3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)NH_2$	20	75+
3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)NHCH_2CH_2C_6H_5$	35	35
3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)NHCH(CH_3)CH_2C_6H_5$	25	25
3-$C_6H_5CH_2O$-4-$CH_3OC_6H_3CH_2CH(CH_3)NH_2$	35	35
3,4-$CH_2O_2C_6H_3CH_2CH(CH_3)NH_2$	2.5	7.5
4-$HOC_6H_4CH_2CH(C_2H_5)NH_2$	10	35
$C_6H_5CH_2CH_2CH(CH)_3NH_2$	15	40
4-$HOC_6H_4CH_2CH_2CH(CH_3)NHC_4H_9$	20	25
4-$HOC_6H_4CH_2CH_2CH(C_2H_5)NH_2$	25	50
3,4-$(CH_3O)_2C_6H_3CH_2CH_2CH(CH_3)NH_2$	25	75
$C_6H_5(CH_2)_3CH(CH_3)NH_2$	6	30
4-$HOC_6H_4(CH_2)_3CH(CH_3)NH_2$	25	50
$C_6H_5(CH_2)_4CH(CH_3)NH_2$	15	25

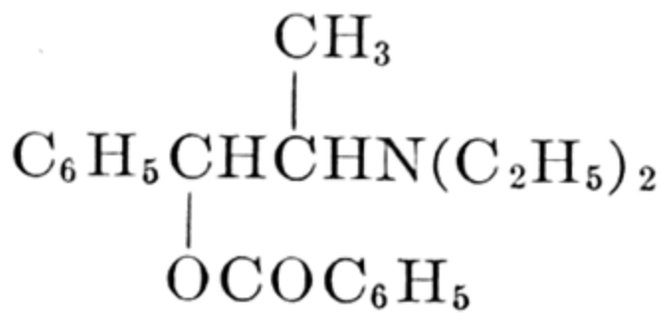
morphine.[115, 116] Epinephrine, when led directly into the brain, causes spectacular and long-lasting analgesia. Many compounds bearing structural resemblance to phenethylamine derivatives and exhibiting analgetic activity have been described in Chapter XI. Attention should be drawn

[115] Fellows and Ullyot, *Abstracts*, First Natl. Medicinal Chem. Symposium, Am. Chem. Soc., Ann Arbor, Mich., 1948.
[116] Goetzl, Burrell, and Ivy, *Proc. Soc. Exptl. Biol. Med.*, **55,** 248 (1944).
[117] Dodds, Lawson, and Williams, *Nature*, **151,** 614 (1943); Proc. Roy. Soc. (London) **B132,** 119 (1944).

here only to products derived from α,β-diphenylethylamine ($C_6H_5CH(NH_2)CH_2C_6H_5$) and α,β-diphenylethanolamine ($C_6H_5CH(NH_2)CHOHC_6H_5$) which relieve pain in cancer patients.[117] These compounds may be regarded as derivatives of phenethylamine and phenylethanolamine containing an aromatic nucleus in place of the more widely tried alkyl branching as shown in Table V. This table also lists a few derivatives said to exert weak to marked analgetic action in laboratory animals.

Fellows and Ullyot[115] have prepared a large number of derivatives of phenethylamines substituted, both in the ring and the side chain, with on the whole the conventional groups (simple alkyls, OH, OR etc.) and tested them for analgetic activity. A few of these materials exhibiting marked effects in the cat are listed in Table VI. None of them have attained therapeutic significance but they offer food for thought about the pharmacological overlapping of discrete chemical structures. Perhaps the most interesting feature of this series may be found in the increasing activity exhibited by α-branched-chain amines in which the amino group is separated from the nucleus by more than two carbon atoms. 2-Amino-4-phenylbutane ($C_6H_5(CH_2)_2CH(CH_3)NH_2$) is more active than amphetamine, and activity reaches a peak in 2-amino-5-phenylpentane ($C_6H_5(CH_2)_3CH(CH_3)NH_2$). A neurotoxic action is the only side-effect which stands in the way of therapeutic usefulness of this drug. The next homolog, 2-amino-6-phenylhexane ($C_6H_5(CH_2)_4CH(CH_3)NH_2$), is much less active.

A transition from pressor to local anesthetic activity is readily found if the alcoholic hydroxyl group of phenylethanolamines is benzoylated. For instance, 1-phenyl-1-benzoyloxy-2-diethylaminopropane (XIX-84) is the local anesthetic Allocaine. It has no longer vasoconstrictor activity.[118]



(XIX-84)

IX. PHYSICAL PROPERTIES AND SYMPATHOMIMETIC ACTIVITY

Only few studies correlating physical and pharmacological properties of adrenergic amines have been reported. It would appear that the basicity of these compounds may be proportional to their activity but this does not seem to be the case.[119] From the tabulation of the data

[118] Alles and Knoefel, *Arch. intern. pharmacodynamie*, **47,** 96 (1934).
[119] Leffler, Spencer, and Burger, *J. Am. Chem. Soc.*, **1951** in press.

TABLE VII. BASICITY AND PRESSOR ACTIVITY OF SYMPATHOMIMETIC AMINES[119]

Name	Formula	pK_b	Pressor Activity
Phenethylamine	$C_6H_5CH_2CH_2NH_2$	9.83	80–250
			125
			183
Vonedrine	$C_6H_5CH(CH_3)CH_2NHCH_3$	9.88	620
			250
Amphetamine	$C_6H_5CH_2CH(CH_3)NH_2$	9.77	200–250
			325
			425
Pervitin	$C_6H_5CH_2CH(CH_3)NHCH_3$	9.87	500–1000
N,N-Dimethylamphetamine	$C_6H_5CH_2CH(CH_3)N(CH_3)_2$	9.40	1000
Paredrine	$4\text{-}HOC_6H_4CH_2CH(CH_3)NH_2$	9.31	50–100
Paredrine methyl ether	$4\text{-}CH_3OC_6H_4CH_2CH(CH_3)NH_2$	9.53	3000
(−)-Ephedrine	$C_6H_5CHOHCH(CH_3)NHCH_3$	9.58	143–333
			250
Neosynephrine	$3\text{-}HOC_6H_4CHOHCH_2NHCH_3$	8.86	5–10
			4
Sympatol	$4\text{-}HOC_6H_4CHOHCH_2NHCH_3$	8.90	25–100
			94
			118
Isuprel	$3,4\text{-}(HO)_2C_6H_3CHOHCH_2NHCH(CH_3)_2$	8.57	Depressor
Cobefrine	$3,4\text{-}(HO)_2C_6H_3CHOHCH(CH_3)NH_2$	8.45	4
			5
			12
Butanefrine	$3,4\text{-}(HO)_2C_6H_3CHOHCH(C_2H_5)NH_2$	8.42	Depressor
1-Cyclohexyl-2-aminopropane	$C_6H_{11}CH_2CH(CH_3)NH_2$	10.14	200
Benzedrex	$C_6H_{11}CH_2CH(CH_3)NHCH_3$	10.52	333–500

TABLE VIII. BASICITY AND DIPOLE MOMENT[120]

Compound	pK_b	Dipole Moment in Dioxane, Debye Units
$C_6H_5CH_2CH_2NH_2$	9.83	1.243
$C_6H_5CH_2CH(CH_3)NH_2$	9.77	1.061
$p\text{-}HOC_6H_4CH_2CH(CH_3)NH_2$	9.31	2.184
$p\text{-}HOC_6H_4CHOHCH_2NHCH_3$	9.90	5.687

[120] Geary and Miller, *J. Electrochem. Soc.*, **97**, 54 (1950).

(Table VIII) it can be seen that the basicities are predictable on the basis of the structure of the compounds. The amines without an oxygen function are more basic than the amino alcohols, and the latter again are more basic than phenolic derivatives. Two phenolic hydroxyls depress the pK_b further.

There appears to be a trend toward increased pressor activity as basicity declines, but on the basis of structure alone one would expect that a compound such as Neosynephrine would have high activity.

In the series Sympatol, Neosynephrine and epinephrine a correlation between basicity and activity is observed, but in other similar series, no such regularity is noted. The few dipole moment values available indicate that low basicity in sympathomimetic amines corresponds to high dipole moment.

CHAPTER XX

Adrenergic Blocking Agents

Drugs which block adrenergic stimulation of muscles and glands have become known as adrenolytic and sympatholytic agents. They do not prevent the release of the sympathetic nervous chemical mediators but they interfere peripherally with the effect of sympathin or block autonomic ganglia ("adrenergic blockade"). The main types of compounds which can accomplish these actions are the ergot alkaloids, ergotoxine and ergotamine, certain basic derivatives of benzodioxane, the drug Priscoline, and the beta-chloroethylamines exemplified by Dibenamine.

There still exists a considerable lack of unanimity of opinion among pharmacologists about the duality of sympathetic blockade. Some blocking agents appear to be specifically directed against the effects of epinephrine while others counteract also the more diffuse effects of (electrical) sympathetic stimulation.[1] Much controversy in the pharmacological literature has centered around these phenomena. It appears, at the time of this writing, that more fundamental knowledge concerning the transmission of sympathetic impulses will have to be gained before the terms adrenolytic and sympatholytic will assume a more discretely defined meaning. The recent discovery of the duality of the natural sympathetic mediator—epinephrine plus norepinephrine—will contribute to clarify these questions.

I. THE ERGOT ALKALOIDS

The dark parasitic fungus ergot (*Claviceps purpurea*) grows on rye particularly during humid summers and has been known to countless civilizations. Before the high toxicity of the material was appreciated, the diseased grain caused veritable epidemics of ergotism expressed by burning sensations and gangrene in the extremities, abortions and convulsions. Under the names of Holy Fire or St. Anthony's fire, ergot poisoning plagued whole populations in all parts of the earth.[2]

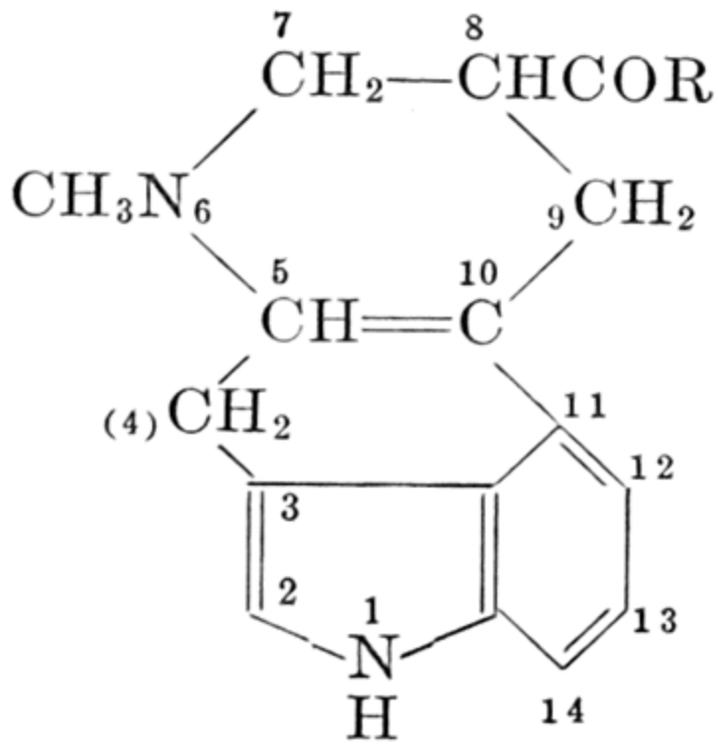
Ergot contains an unusually large number of pharmocodynamically active substances. One group comprises about ten alkaloids which are

[1] Yonkman, Stilwell, and Jeremias, *J. Pharmacol. Exptl. Therap.*, **81,** 111 (1944). Nickerson, *ibid.*, **95,** 27 (1949).

[2] Barger, *Ergot and Ergotism.* Guerney and Jackson, Edinburgh, 1931.

regarded as five pairs of optical isomers. Of these, three levorotatory compounds possess the uterus-contracting and other valuable properties of ergot. Besides, ergot contains various primary amines, especially histamine, isoamylamine and tyrosine, as well as the quaternary ammonium bases, choline and acetylcholine. It is not surprising that the fungus with all its self-contradictory drugs has been an intriguing material for pharmacological research.

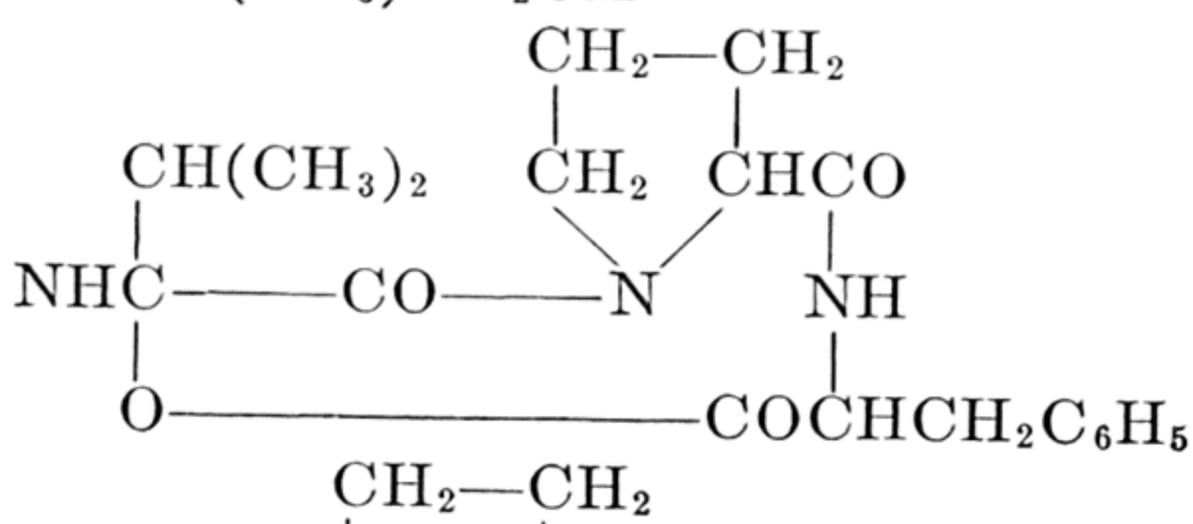
The three pharmacodynamically most valuable ergot alkaloids, ergotoxine (XX-1), ergotamine (XX-2) and ergonovine (XX-3) are amides or peptides of a common parent compound, lysergic acid (XX-4). The structure of lysergic acid has been deduced from degradation reactions, and 5,10-dihydrolysergic acid has been synthesized.[3] The structure of ergonovine and its *d*-isomer, ergometrinine has been recognized as 2-(1-hydroxypropyl) lysergamide. The other drugs, ergotamine and ergotoxine, are peptides of which the sequence and internal arrangement of the peptide



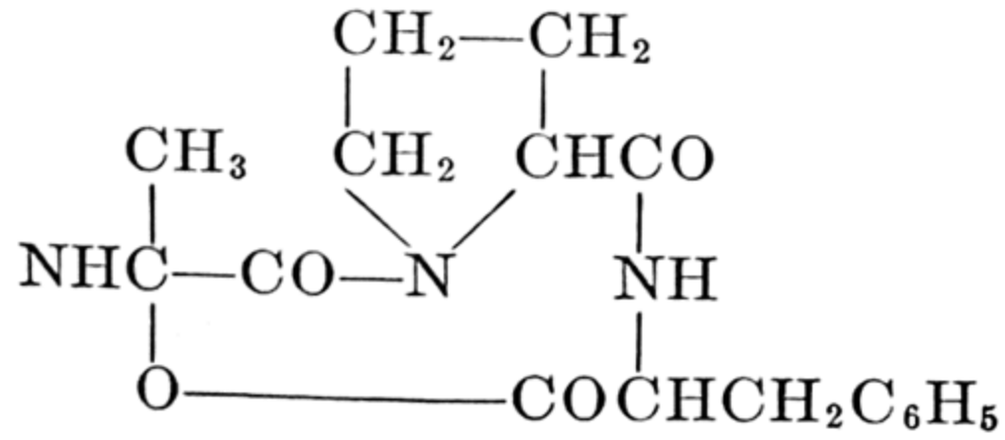
(XX-4): R = OH

(XX-3): R = $NHCH(CH_3)CH_2OH$

(XX-1):



(XX-2):



[3] Uhle and Jacobs, *J. Org. Chem.*, **10,** 76 (1945).

groups has not yet been ascertained. A recent short review of the chemistry of this series has been presented by Stoll.[4]

The structure of the simplest peptide-like derivative of lysergic acid, ergonovine, can be imitated readily in semisynthetic analogs. They are obtained by treating lysergyl chloride with the corresponding amines or amino alcohols. The most active of these compounds is methergine (XX-5, R = $NHCH(C_2H_5)CH_2OH$) which is about thirty per cent more potent than ergonovine and can be used orally as an oxytocic.[5]

Hydrogenation of the 5,10-double bond in the lysergic moiety of the ergot bases produces some potent and, sometimes, less toxic dihydro derivatives. This holds only for the polypeptide-type compounds while the simple alkaloidal derivative (dihydroergonovine) is almost without effect. Unfortunately dihydro derivatives retain much of the centrally stimulating action, and excite especially the emetic center.

Using the seminal vesicle of an adult guinea pig for assaying the ability of the drugs to prevent contraction provoked by a 1 x 10^{-6} solution of epinephrine, the following sympatholytic activities were observed.[6]

Ergotamine = 1	Dihydroergotamine = 7
Ergocornine = 2	Dihydroergocornine = 25
Ergocristine = 4	Dihydroergocristine = 35

The pharmacological action of ergotoxine and ergotamine may be circumscribed by their ability to inhibit, and block all responses to the stimulation of adrenergic nerves, but large doses may lead to a rise in blood pressure. Ergonovine, on the other hand, is not a true sympatholytic drug, but overlaps in some of its reactions with adrenergic amines. It produces mydriasis in the rabbit's eye, constricts blood vessels and relaxes isolated strips of gut. However, it does not raise the blood pressure of anesthetized laboratory animals.

Ergot alkaloids are also used in obstetrical practice as uterine contractants (oxytocics) to induce labor and control uterine hemorrhages. They are often administered as soluble salts of organic acids such as tartrates, ethanesulfonates, etc.

Ergonovine elicits the most rapid response. It is well absorbed from the gastro-intestinal tract and is therefore active when given by mouth. The absence of multiple peptide linkages in its formula may account for this stability.

Ergotamine, and especially its 5,10-dihydro derivative, dihydroergotamine, as well as dihydroergocornine are probably the most effective drugs

[4] Stoll, *Experientia*, **1,** 250 (1945).
[5] Bachbauer, *Geburtshilfe und Frauenheilkunde*, **6,** 278 (1944).
[6] Brugger, *Helv. Physiol. et Pharmacol. Acta*, **3,** 117 (1945).

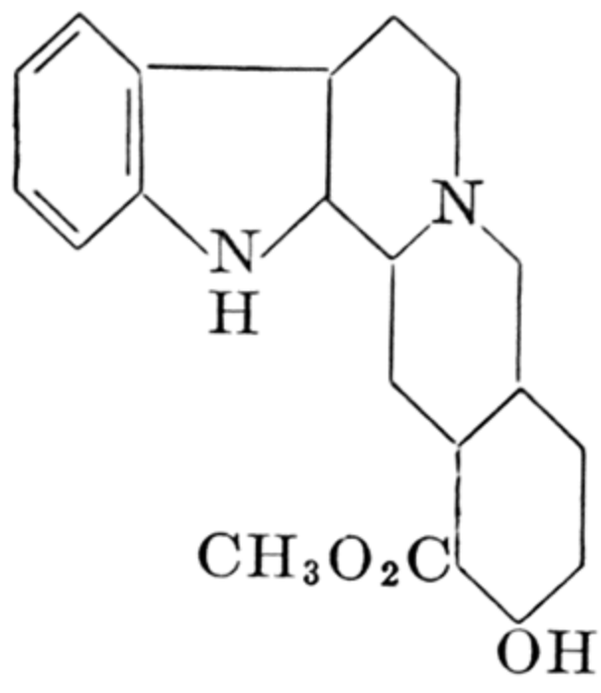
known for the symptomatic relief of migraine headaches. Pain in this condition is due to cranial vasodilation following vasoconstriction.[6a] None of the theories which attempt to arrive at a pharmacological explanation of the therapeutic activity of ergotamine in this condition have been satisfactory. Ergonovine is much less reliable than ergotamine.[7] None of the alkaloids can be used prophylactically because they produce symptoms of cumulative toxicity identical with the historic ergotism.

II. YOHIMBINE

Yohimbine is the best-known alkaloid obtainable by extraction of the tropical yohimbehé or quebracho barks. Its molecular composition $C_{21}H_{26}N_2O_3$ has been resolved to the formula (XX-6) through the researches of Barger, of Scholz and of Witkop.[8]

Yohimbine possesses a variety of pharmacodynamic properties ranging from vasodilator and respiratory stimulant to local anesthetic actions. Its vasodilator activity is particularly pronounced in the blood vessels of the genital organs which, under its influence, are perfused by unusually large amounts of blood and are thereby stimulated. The alkaloid has therefore been used as an aphrodisiac. It also reverses the actions of epinephrine and was one of the first drugs to be studied as a sympatholytic.

Because of its high systemic toxicity and its diversified actions which appear as unwanted side-effects when yohimbine is administered for a special purpose, the alkaloid is no longer used in medicine. A study of its congeners and derivatives in regard to their sympatholytic activity may be found in Henry's treatise.[8]



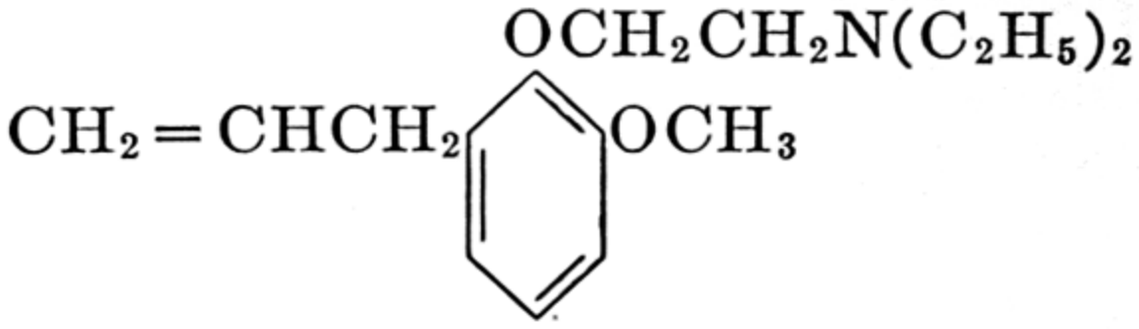
(XX-6)

[6a] Marcussen and Wolff, *Arch. Neurol. Psychiatry*, **63,** 42 (1950).
[7] Goodman and Gilman, *The Pharmacological Basis of Therapeutics*. Macmillan, New York, 1941, p. 482 ff.
[8] Henry, *The Plant Alkaloids*, 4th ed. Blakiston, Philadelphia, 1949, p. 500.

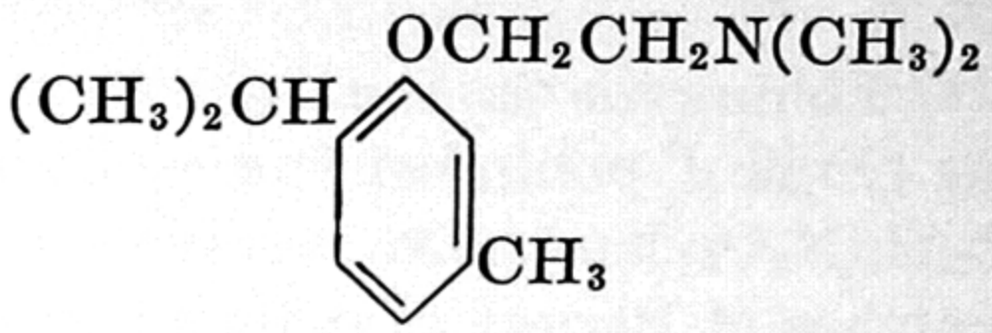
III. AMINOALKYL ARYL ETHERS

1. The Early French Drugs

During their general screening programs for compounds of oxytocic character, several investigators had noticed uterus-relaxant properties in several series not related to the ergot alkaloids. Two aminoalkyl phenyl ethers, Gravitol (XX-7) and Tastromine (XX-8) were singled out as promising examples which appeared to provide a new lead in this field.[9]



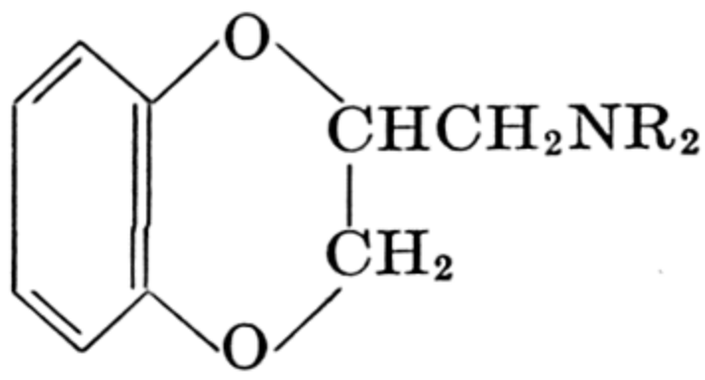
(XX-7)



(XX-8)

This hope was fully realized in the work of Fourneau, Bovet, Staub and their associates at the Pasteur Institute. It led to more potent adrenergic blocking agents and provided the entering wedge into the field of antihistaminics[10] (Chapter XXIV).

The immediate outcome of these studies was the synthesis of adrenolytic aminoalkyl benzodioxane derivatives (XX-9) which could be evaluated experimentally in human diseases although their high toxicity was prohibitive for general therapeutic usage. One of them, 2-piperidinomethyl-1,4-benzodioxane (XX-9, $NR_2 = NC_5H_{11}$) is indicated in Raynaud's dis-



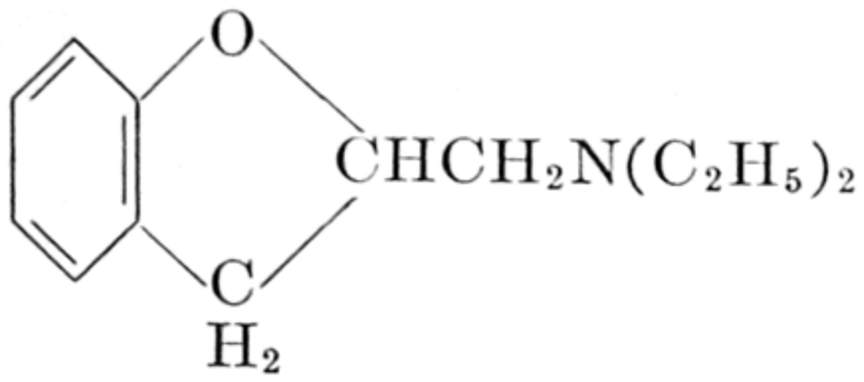
(XX-9)

ease[11] and sclerodermia, and the corresponding diethylamino derivative ($NR_2 = N(C_2H_5)_2$, Prosympal) has good sedative properties in angina pectoris.

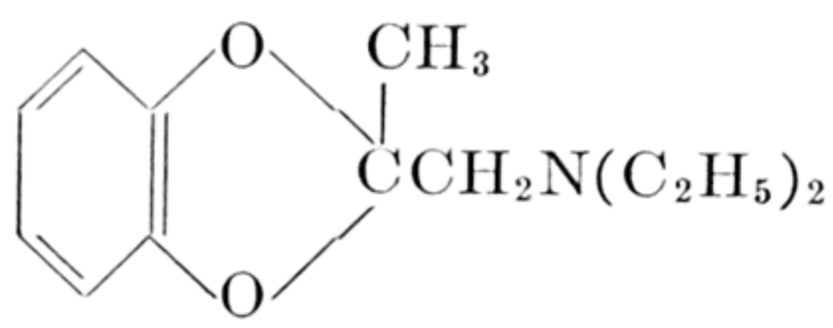
Some structural variations involving the replacement of the benzodioxane system by benzoxazine, quinoxaline, benzothiazine and benzoxazole

[9] Anan, *Folia Pharmacol. Japon.*, **9,** 53 (1929); *Ber. ges. Physiol.*, **53,** 430 (1930).
[10] Fourneau, Maderni, and Lestrange, *J. pharm. chim.*, **18,** 185 (1933).
[11] Bovet and Simon, *Compt. rend. soc. biol.*, **117,** 1011 (1934). *Chem. Abstr.*, **29,** 1877 (1935). Sterne, *Ann. méd.*, **42,** 541 (1937). *Chem. Abstr.*, **32,** 1403 (1938).

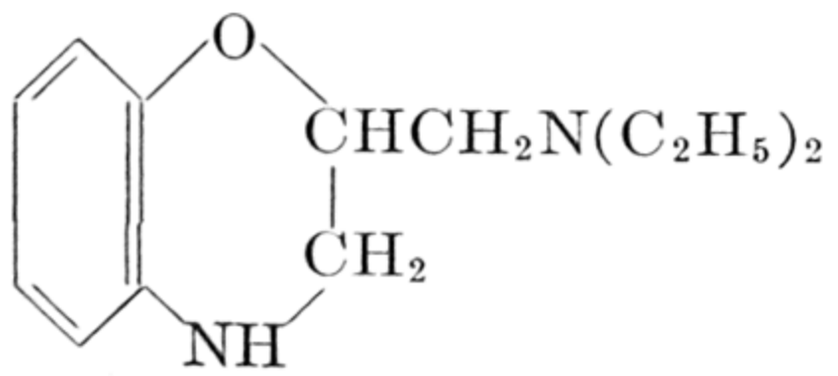
were studied by Bovet.[12] The compounds were vasodepressors, and most of them were sympatholytics. Their formulas and names are listed below.



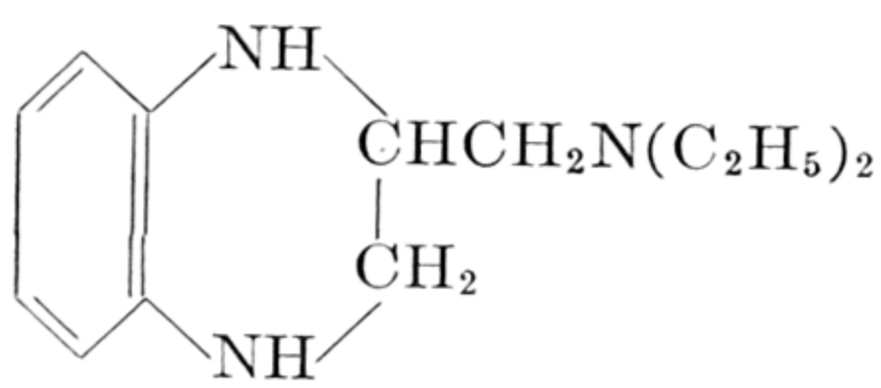
2-Diethylaminomethylcoumaran



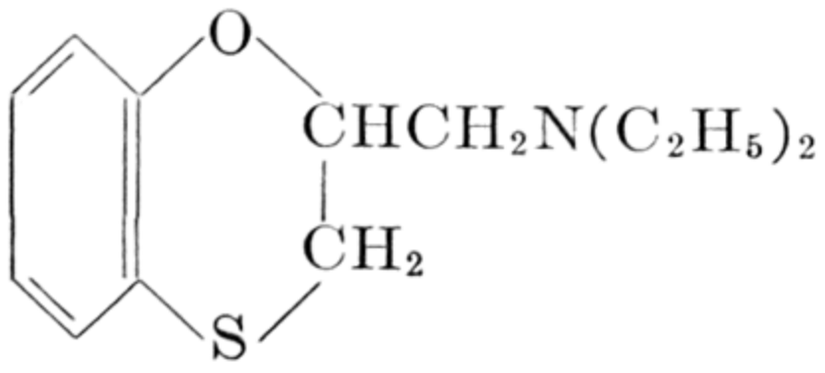
1-Dimethylamino-2-(*o*-phenylenedioxy)propane



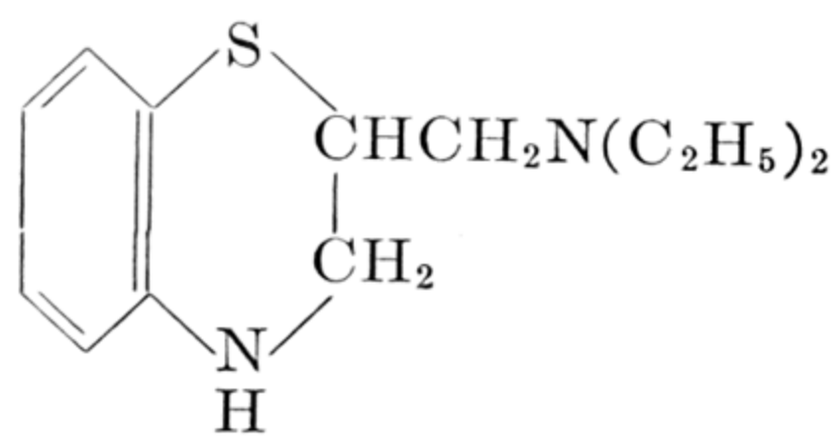
3-Diethylaminomethylbenzomorpholine



2-Diethylaminomethyl-1,2,3,4-tetrahydroquinoxaline



2-Diethylaminomethylbenzothioxane



2-Diethylaminomethyl-2,3-dihydrobenzothiazine

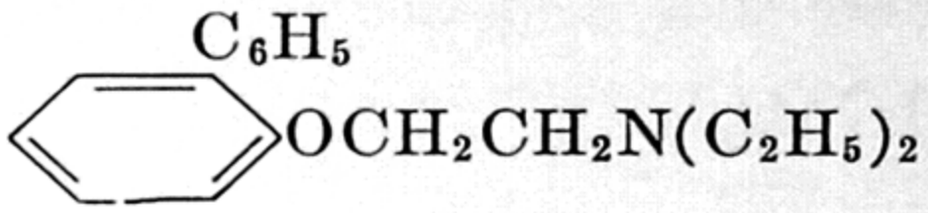
Throughout the series of sympatholytic ethers, increased antiadrenergic properties are usually accompanied by increased toxicity. Most of the compounds are hypotensive, but exceptions to this rule are numerous, and no definite predictions about their vasopressor qualities can be made.

2. Antifibrillants

In a general way, sympatholytic drugs diminish excitability, particularly of the heart muscle. This suggests their use as antifibrillants which could counteract the irregular heart rhythm known as ventricular fibrillation.

[12] Fourneau, Bovet, and Maderni, *Compt. rend. soc. biol.*, **115,** 1215 (1934). Benoit and Bovet, *J. Pharm. Chim.*, (8) **22,** 544 (1935); *Bull. Soc. Pharmacol.*, **45,** 97 (1938).

A series of basic alkyl biphenyl ethers has been tested in this condition, and 2-β-diethylaminoethoxybiphenyl (Dacorene, XX-10) has been found to possess desirable antifibrillant properties.[13]

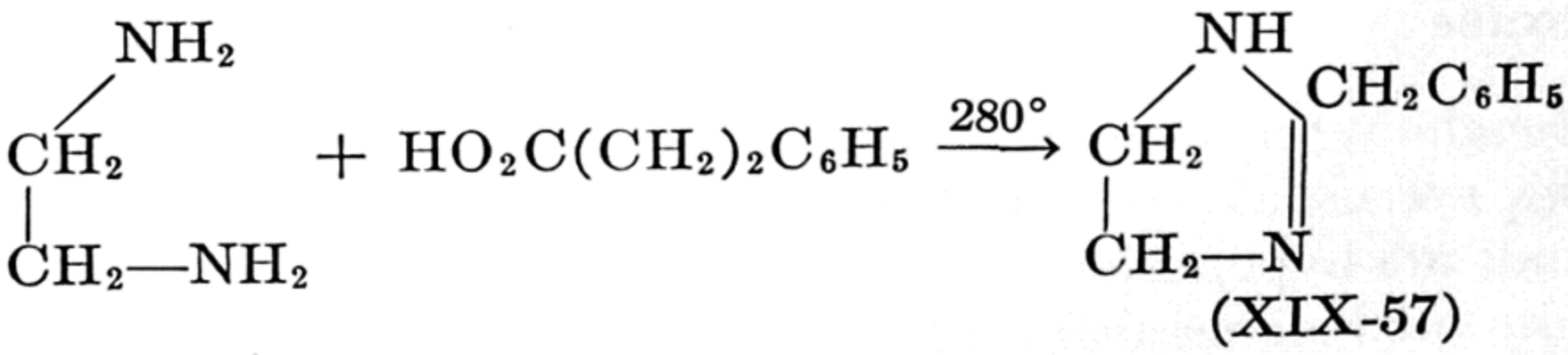


(XX-10)

Other compounds which have shown promise as antifibrillants are the fagarins, alkaloids from the South American plant, *Fagaro coco* (Gill) Engl.[14] Several analogs of the antispasmodic drug Sestrone (XXIII-31) have also been tested.

IV. 2-BENZYLIMIDAZOLINE (PRISCOLINE)

The same overlapping of vasoconstrictive and vasodilatory properties is observed in the series of aralkylimidazolines. It will be remembered that Privine, 2-(α-naphthylmethyl)imidazoline, is an excellent vasoconstrictor of low toxicity (XIX-59). The analogous 2-benzylimidazoline (XIX-57) has the opposite effect; it is a useful though not highly specific vasodilator. Introduced under the names of Benzazoline or Priscoline, it is, in larger doses, a good non-toxic sympathetic blocking agent of short duration of action. It also relieves angiospasm (spasm of thoracic blood vessels, angina pectoris), and has been used in Buerger's and Raynaud's disease, in ulcers caused by poor circulation, and in other diseases which can be traced to insufficient flow of blood due to vasoconstriction. It also relieves pain and spasms in acute anterior poliomyelitis.[15]

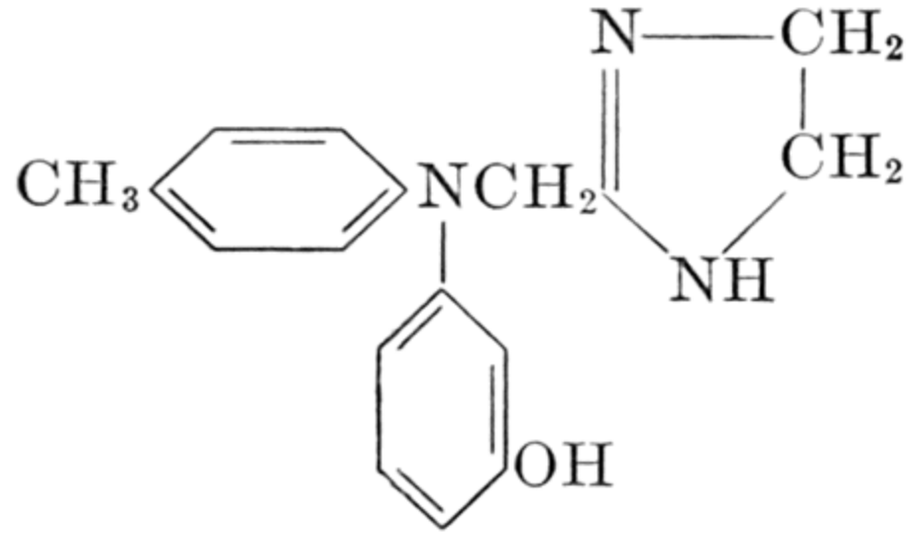


(XIX-57)

Priscoline is synthesized by heating ethylenediamine and beta-phenylpropionic acid according to the preceding scheme.[16] N^1-Methylpriscoline is a vasopressor which stimulates sympathetic ganglia.[16a]

[13] Bovet, Fourneau, Tréfouël, and Strickler, *Arch. int. Pharmacodynamie*, **62,** 234 (1939).
[14] Deulofeu, Labriola, and Langhe, *J. Am. Chem. Soc.*, **64,** 2326 (1942).
[15] Smith, Graubard, Goldstein, and Bikoff, *N. Y. State J. Med.*, **48,** 2608 (1948).
[16] Scholz, *Ind. Eng. Chem.*, **37,** 120 (1945).
[16a] Gowdey, *Brit. J. Pharm. Chemotherap.*, **3,** 254 (1948).

Another potent adrenergic blocking agent containing the imidazoline ring has recently been announced.[17] This compound, 2[N-*p'*-tolyl-N-(*m'*-hydroxyphenyl)aminomethylimidazoline (XX-11) can also be regarded as a diphenylamine derivative not entirely unrelated to certain antihistaminic drugs.



(XX-II)

V. β-CHLOROETHYLAMINES

The most interesting development in sympatholytics grew out of the chance observation that β-chloroethyl-dibenzylamine hydrochloride ($ClCH_2CH_2N(CH_2C_6H_5)_2 \cdot HCl$, Dibenamine) produces complete adrenergic blockade in laboratory animals.[18] The compound, first prepared by Gump in the course of some unrelated work on quaternary ammonium salt antiseptics, is quantitatively less sympatholytic than the ergot alkaloids, yohimbine or the aminomethyl benzodioxane derivatives discussed above, but the long duration of its effect as well as the overall blocking of sympathetic stimulation have encouraged extensive studies of Dibenamine. The drug is not the most potent and least toxic among many analogs but has given a picture of the potential usefulness of this series.

Among the clinical conditions benefited by Dibenamine are the many symptoms and diseases which are caused by over-excitement by hormonal Adrenalin. Vasoconstriction, often resulting in diminished flow of blood in the extremities with an accompanying feeling of cold and occasional gangrene in these organs, is effectively combatted by sympatholytic drugs. Dibenamine, combined with warming-up of frozen limbs, provides the best treatment for frostbite yet discovered. Raynaud's disease, symptomized by painful discoloration of the skin, is ordinarily treated by removing sections of the sympathetic system innervating the afflicted areas. Dibenamine approaches in its effects this radical surgical procedure. Scleroderma and thrombophlebitis are similar conditions benefited by this drug;

[17] Warren, Woodbury, and Trapold, *Federation Proc.*, **8,** 343 (1949).
[18] Nickerson and Goodman, *Federation Proc.*, **5,** 194 (1946); *J. Pharmacol. Exptl. Therap.*, **89,** 167 (1947).

cerebral vascular spasms, which lead to a pathological deficiency of blood in the brain and thereby inhibit the active respiration of this organ, are relieved by relaxation of the blood vessels under the anti-adrenergic effect of the drug. It has also been tried to reduce intraocular pressure in glaucoma.

Although Dibenamine does not antagonize stimulation of the heart by epinephrine, it does prevent fibrillation, that is, irregular cardiac action often encountered for instance after cyclopropane anesthesia. In the field of psychiatry, Dibenamine helps to overcome anxiety states caused by excess adrenergic compounds, especially Adrenalin, in the circulation.

Dibenamine (XX-12) is synthesized from dibenzylamine and ethylene chlorohydrin, followed by conversion of the amino alcohol (XX-13) to the chloride hydrochloride with thionyl chloride.

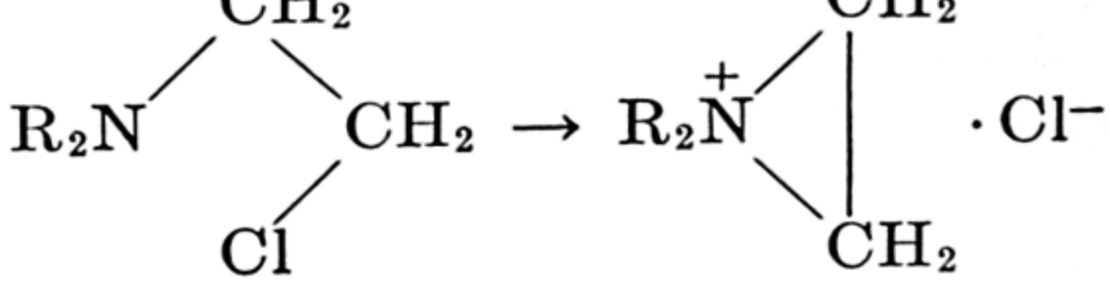
$$(C_6H_5CH_2)_2NH + ClCH_2CH_2OH \rightarrow (C_6H_5CH_2)_2NCH_2CH_2OH$$

(XX-13)

$$\rightarrow (C_6H_5CH_2)_2\overset{+}{N}HCH_2CH_2Cl \cdot Cl^-$$

(XX-12)

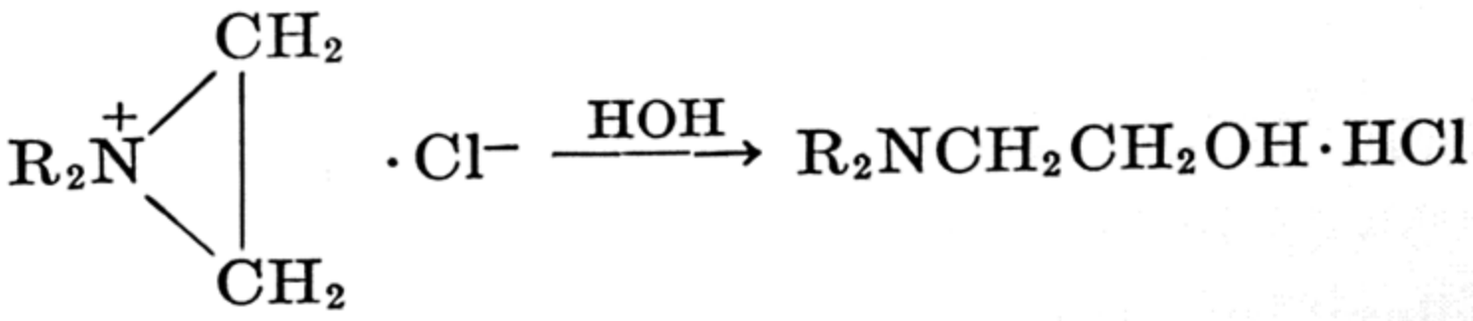
It is stable as the salt only; the free base soon undergoes intramolecular cyclization with formation of an ethyleneiminium ion (XX-14).



(XX-14)

The rate of cyclization in such compounds depends on the nature of the alkyl substituents. It was thought, at first, that the sympatholytic activity of Dibenamine analogs may be related to this rate. However, no relation of ethyleneiminium ion concentration to activity could be elaborated.

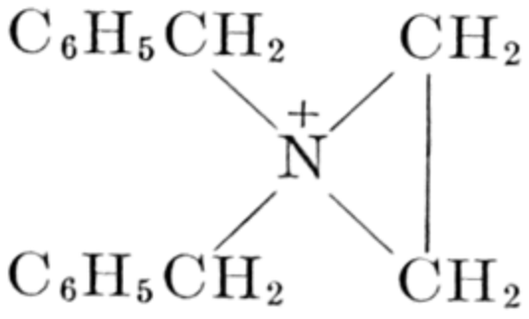
The chemical role of ethyleneiminium ions is well understood; the ions act as alkylating agents for many types of reactive compounds. With water, for instance, the strained ring is hydrolyzed, and aminoalcohols are obtained.



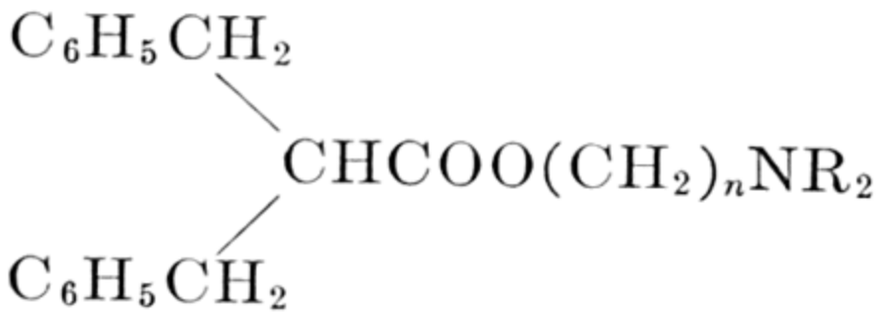
This reaction may well be the cause of inactivation *in vivo*. Most of the chloroethyldialkylamines are active only on intravenous injection but inactive, or barely active orally. It is perhaps the persistance of some of

the cyclic ions, determined by the alkyl substituents, which causes the occasionally observed oral activity.

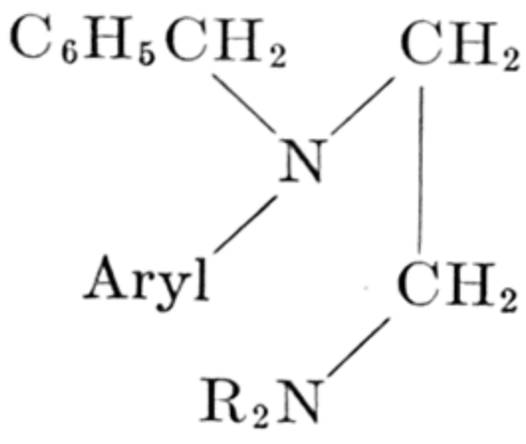
It is idle to speculate what the exact *in vivo* physiological reaction of dibenzyl-β-chloroethylamine may be. It has been shown *in vitro* that its antagonistic effect on Adrenalin is not due to direct interaction with the pressor hormone. There is no reason to assume that there would be a direct reaction between the two substances *in vivo*. The drug—or its analogs—are undoubtedly transformed to the cyclic ions in the animal, and these ions may alkylate sulfhydryl groups, amino groups etc. of proteins or enzymes at the receptor organs to stable compounds, thus changing their susceptibility to epinephrine. As a matter of definition, any selective alkylating agent for proteinogenous groups may act as a sympatholytic agent, provided its pharmacological properties (solubility, absorption, distribution, excretion, toxicity, etc.) make it suitable as a drug. It should be observed that there is an unmistakable similarity in the "steric fitting" at the place of action between dibenzyl-ethyleneiminium ions (XX-15), the esters of dibenzyl acetic acid, (XX-16), and the antihistaminic agents of the benzhydryl (XX-17) or benzylaniline types (XX-18) which all antagonize, fundamentally, two spasmogenic agents, acetylcholine and histamine.



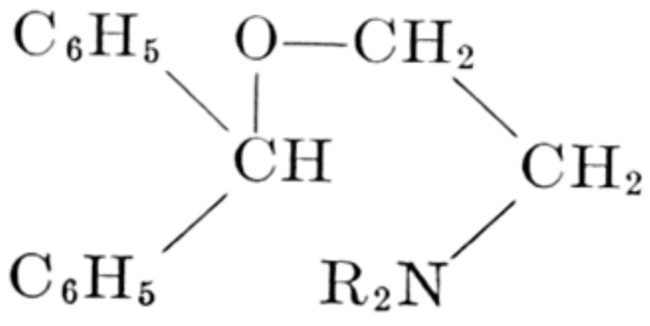
(XX-15)



(XX-16)



(XX-18)

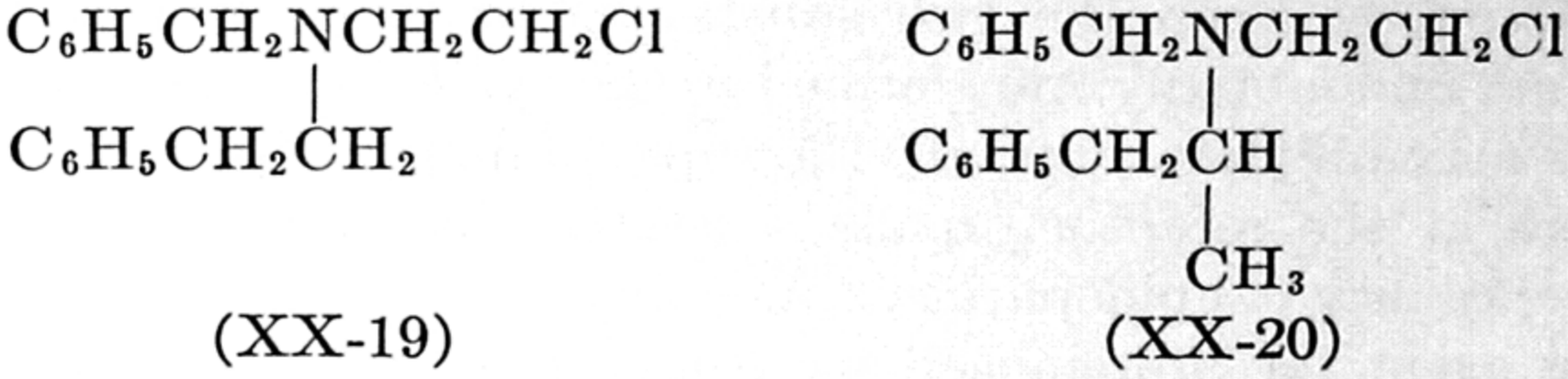


(XX-17)

There have been numerous modifications of the dibenzyl-β-chloroethylamine structure, and some of the compounds in this series point to the possibility that drugs of considerably higher potency, and of lower toxicity than Dibenamine may be expected to be introduced into therapy.

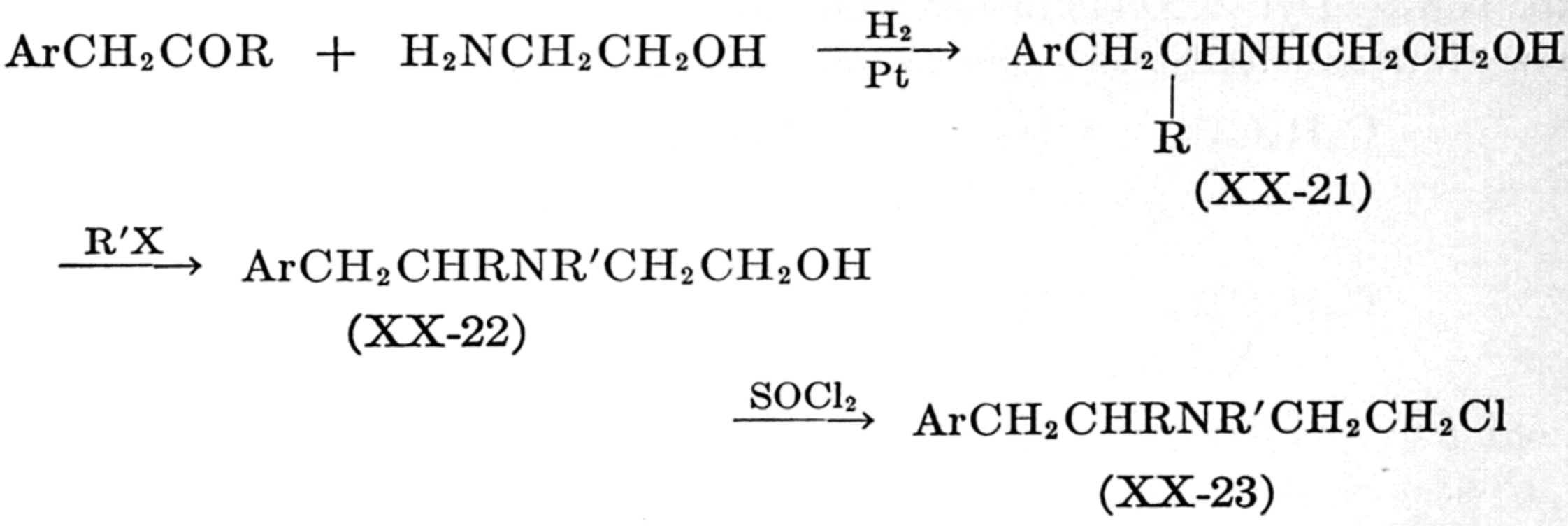
Activity depends on the presence of a β-chloroethylamino group with a tertiary amine nitrogen substituted by suitable aralkyl groups. β-Chloroethyl-benzylamine ($C_6H_5CH_2NHCH_2CH_2Cl$) is inactive, as is dibenzyl-ethylamine ($(C_6H_5CH_2)_2NC_2H_5$) and, significantly, dibenzyl-γ-chloropropylamine ($(C_6H_5CH_2)_2NCH_2CH_2CH_2Cl$). The latter is apparently unable of being cyclized to unstable iminium ions.

When one of the benzyl groups of Dibenamine is replaced by phenethyl (XX-19), activity is affected adversely. However, branching of the phenethyl group not only restores but increases sympatholytic properties (XX-20). Substitution of the aromatic ring of the phenylisopropyl group by phenolic hydroxyl, or by methoxyl groups brings about a very pronounced rise in potency, and even oral activity.[19]



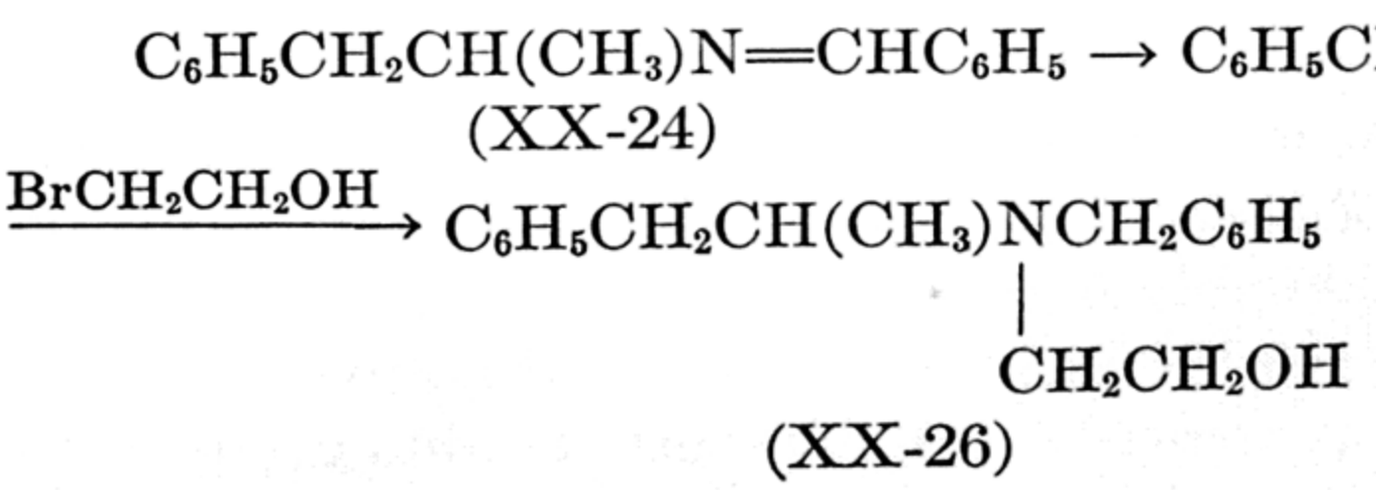
(XX-19) (XX-20)

The methods for the preparation of these compounds employ the reductive amination of benzyl alkyl ketones with ethanolamine, treatment of the secondary-amino alcohol (XX-21) with alkyl halides, and conversion of the tertiary-amino alcohol (XX-22) to the chloride (XX-23) by means of thionyl chloride.



(XX-21) (XX-22) (XX-23)

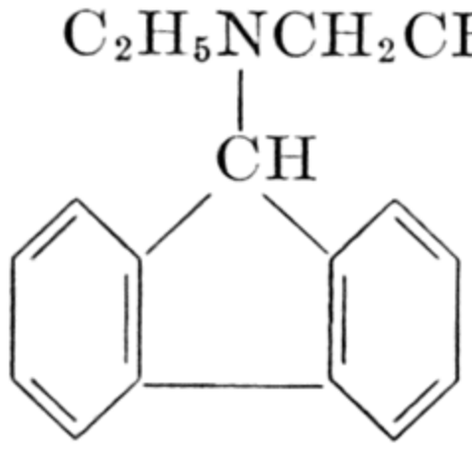
Alternately, the benzal derivative of Benzedrine (XX-24) can be reduced to the corresponding benzyl compound (XX-25) which is then treated with ethylene bromohydrin to give the amino alcohol (XX-26).



(XX-24) (XX-25) (XX-26)

[19] Kerwin, Herdegen, Heisler, and Ullyot, *Abstracts*, 116th Meeting, Am. Chem. Soc., Atlantic City, N. J., Sept. 1949, p. 23I. Ullyot, Kerwin, Fellows, and Macko, *Federation Proc.*, **8,** 340 (1949); Kerwin, Ullyot *et al.*, Abstracts, 118th Meeting, Am. Chem. Soc., Chicago, Sept. 6, 1950, p. 26M.

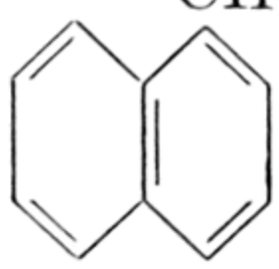
N-Ethyl-N-(β-chloroethyl)-9-fluorenylamine (XX-27) was ten times as active as Dibenamine and less toxic.[20] As can be seen from its formula, the compound contains a combination of the two benzyl groups in a cyclic benzhydryl group; the amine is tertiary but the large fluorenyl radical is



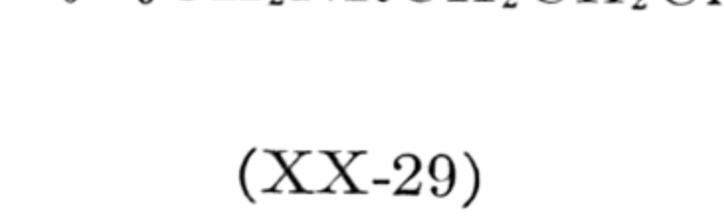
(XX-27)

compensated by the small ethyl group; larger alkyl groups in the same molecular arrangement decrease activity. A corresponding benzhydryl compound, N-ethyl-N-(2-chloroethyl)-benzhydrylamine $[(C_6H_5)_2CHN(C_2H_5)CH_2CH_2Cl]$ is similar to Dibenamine in potency, duration and specificity. Its toxicity is low, and it has little antihistaminic activity.[22]

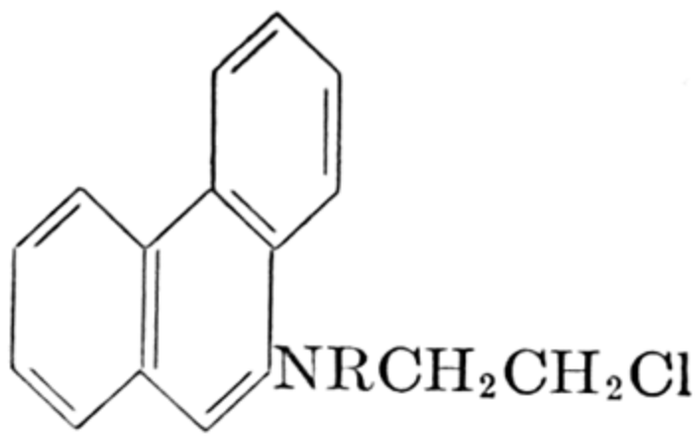
The α-naphthylmethyl-(XX-28), benzyl-(XX-29), 9-phenanthryl-(XX-30), and the *p*- and *m*-xenoxyethyl-[(XX-31) and (XX-32)] derivatives have been tested with wide variations in the alkyl group R. Some of these compounds exhibit both adrenolytic and antihistaminic properties[21] on oral administration.



(XX-28)



(XX-29)

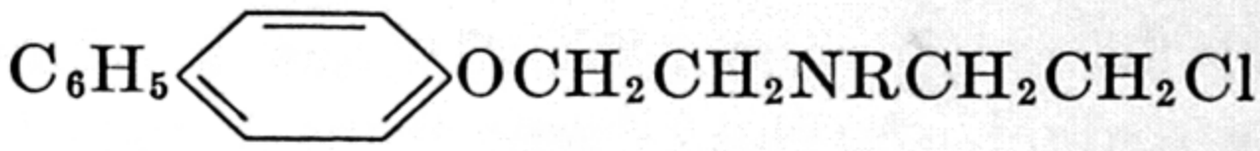


(XX-30)

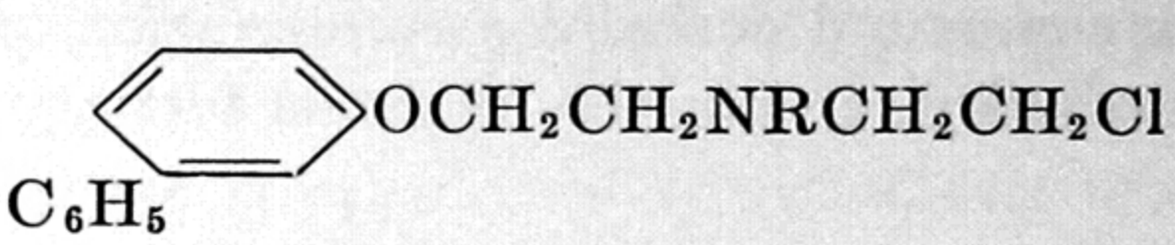
[20] Kerwin, Herdegen, Heisler, and Ullyot, *J. Am. Chem. Soc.*, **72,** 940 (1950). Kerwin, Ullyot, Fellows, and Macko, *Federation Proc.*, **8,** 308 (1949).

[21] Rieveschl, Fleming, and Coleman, *Abstracts*, Meeting, Am. Chem. Soc., New York, Sept. 17, 1947. Rieveschl and Fleming, U. S. Pat. 2,495,772 (1950). Aschenbach and Loew, *Federation* Proc., **6,** 304 (1947).

[22] Loew, Aschenbach, and Micetich, *J. Pharmacol. Exptl. Therap.*, **97,** 441 (1949).

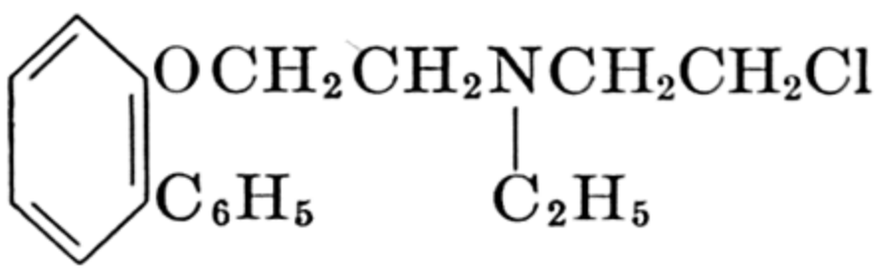


(XX-31)

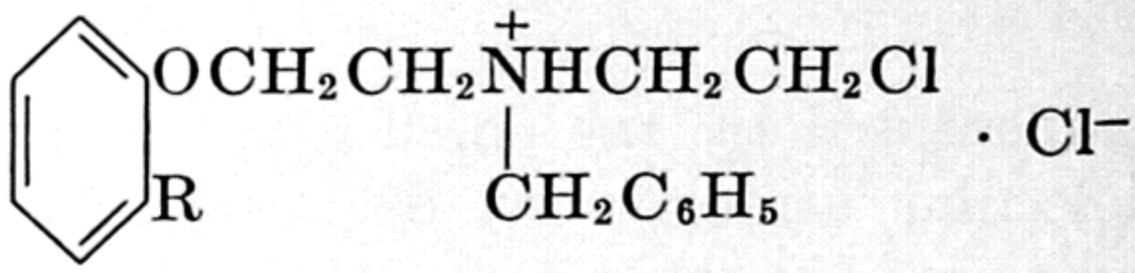


(XX-32)

The *o*-xenoxyethyl compound (XX-33) has pointed again to the potentialities of the aminoalkyl aryl ether structure in sympatholytic research.[21]



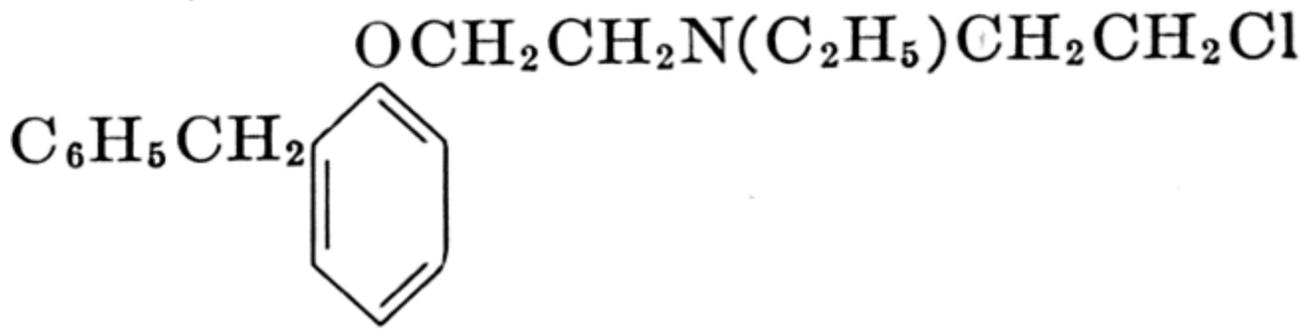
(XX-33)



(XX-34)

Similar compounds combining these features with the benzylamine group encountered in Dibenamine have been reported recently,[23] the least toxic and at the same time most potent adrenergic blocking agent being represented by formula (XX-34, R=CH_3, C_2H_5, $CH(CH_3)_2$).

The *o*-benzylphenoxy derivative (XX-35) is orally active and a good adrenergic blocker, but inevitably causes nausea.[24]



(XX-35)

[23] Gump and Nikawitz, *Abstracts*, Meeting, Am. Chem. Soc., Atlantic City, N. J., September, 1949, p. 221.

[24] Henderson and Chen, *Federation Proc.*, **8,** 301 (1949).

CHAPTER XXI

Parasympathetic Stimulants

I. ACETYLCHOLINE

An extirpated involuntary muscle liberates, under proper experimental conditions, a substance which Loewi called vagus substance.[1] The perfusion liquid containing this material reproduces the effects of parasympathetic stimulation in another similar muscle (frog or mammalian heart) when such an organ is immersed in it.

The nature of the vagus substance suggested itself on the basis of earlier studies of Hunt[2] and of Dale.[3] Adrenal extracts from which epinephrine has been removed cause a fall in blood pressure, and Hunt identified choline in these extracts. He suggested that a readily hydrolyzable ester of choline might be the vasodepressor agent, and called attention to the fact that injected acetylcholine was 100,000 times more active than choline. Dale observed that acetylcholine mimicked the effects of stimulation of the parasympathetic nervous system. He called acetylcholine therefore a parasympathomimetic agent.

Identification of acetylcholine ($CH_3COOCH_2CH_2N^+(CH_3)_3 \cdot OH^-$) as the vagus substance or "parasympathin" rested on both chemical and physiological tests such as the quick hydrolysis in alkaline solution, the stability of acetylcholine to hot dilute acids, and the blocking effect of certain alkaloids on some phases of the physiological activity of acetylcholine. All these tests gave identical results with "parasympathin."

Acetylcholine is hydrolyzed rapidly to acetic acid and to the pharmacologically almost inert choline ($HOCH_2CH_2N^+(CH_3)_3OH^-$) under the influence of the enzymes of the cholinesterase group which are widely distributed in the tissues. There are probably many cholinesterases. One of them, pseudocholinesterase, has been separated cataphoretically.[4] The rate of hydrolysis of acetylcholine is so very high that it can explain the extremely rapid destruction of the ester as it is released by nervous im-

[1] Loewi, *Arch. ges. Physiol.*, **189,** 239 (1921).
[2] Hunt and Taveau, *Brit. Med. J.*, **2,** 1788 (1906). Hunt, *Am. J. Physiol.*, **3,** 18 (1899).
[3] Dale, *J. Pharmacol. Exptl. Therap.*, **6,** 147 (1914).
[4] Augustinsson, *Nature*, **156,** 303 (1945).

pulses. The amount of cholinesterase present in one autonomic ganglion has been calculated to be able to hydrolyze 2 x 10^{12} molecules of acetylcholine in one thousandth of one second.[5] Obviously, acetylcholine must exist in the tissues in an inactive, insoluble and nonhydrolyzable form which is converted to the labile hydrolyzable substance by a nervous impulse. The nature of the inert precursor is not clear; it may be that the quaternary ammonium group is linked firmly to an insolubilizing proton acceptor of the cell chemicals. It is now reasonably certain that liberation of acetylcholine is followed by liberation of potassium ions at the nervous synapse.

When acetylcholine is released by preganglionic nerve fibers, it stimulates ganglion cells in high dilutions and then paralyzes them at higher concentrations. The highly toxic, and therefore therapeutically useless tobacco alkaloid nicotine blocks these effects. The excitation of nervous ganglia and also of (voluntary) skeletal muscles by acetylcholine has often been referred to as its nicotinic action. Part of the nicotinic action of acetylcholine is abolished, in turn, by the active alkaloids of the South American arrow poison curare, which paralyze voluntary muscles and thereby block their stimulation by acetylcholine.

The paralyzing component of acetylcholine action on smooth muscles and glands can be imitated by the alkaloid muscarine. This compound occurs in the poisonous mushroom *Amanita muscaria* together with choline to which it bears a certain structural resemblance. Muscarine is most probably 2-hydroxyvaleraldehyde-3-trimethylammonium hydroxide[6] (XXI-1, $OCHCHOHCH(C_2H_5)N^+(CH_3)_3 \cdot OH^-$).

Both acetylcholine and muscarine produce experimental spasm of surviving extirpated muscles. Drugs which counteract this paralysis, atropine and the antispasmodics, are said to block the muscarinic action of acetylcholine. Vice versa, mushroom poisoning caused by muscarine can be treated successfully with atropine.

The energy necessary for the transmission of the nervous impulse is produced by a reaction of acetylcholine with phosphocreatine. This reaction is catalyzed by an enzyme which competes with cholinesterase for acetylcholine. This relationship ties in the fate of acetylcholine with glucose metabolism.[7]

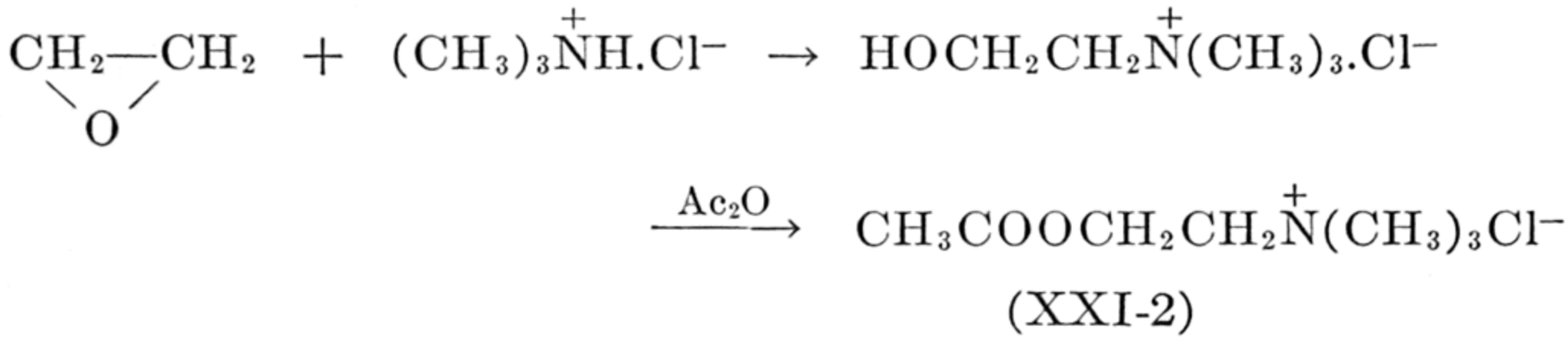
The organ most sensitive to acetylcholine is the isolated heart of *Venus mercenaria* which is stimulated at the unique dilution of 1:15 billions.

[5] Nachmansohn and Marnay, *J. Physiol.*, **92,** 37 (1938). Nachmansohn, *Yale J. Biol. Med.*, **12,** 565 (1940).

[6] Kögl, Duisberg, and Erxleben, *Ann.*, **489,** 156 (1931). Kögl, Veldstra, and Van der Laan, *Ann.*, **552,** 1 (1942).

[7] Rapp, *Arch. Biochem.*, **12,** 13 (1947).

For pharmacological experimentation, and for clinical trials, acetylcholine (XXI-2) has been supplied synthetically. Its first synthesis was recorded by Baeyer;[8] the best method now in use utilizes addition of trimethylammonium chloride to ethylene oxide, followed by treatment of the resulting choline salt with acetic anhydride. The drug is used as the chloride or bromide.



(XXI-2)

The activities of acetylcholine which could become useful clinically are of such short duration that acetylcholine has had little chance as a valuable therapeutic agent. It is too rapidly removed hydrolytically by cholinesterase. However, its ability to stimulate deficient parasympathetic body structures to normal levels of functioning, is a highly desirable property in the treatment of diseases of cholinergic nerves, e.g., the severe muscular collapse called myasthenia gravis. Therefore, many esters having structures similar to acetylcholine have been synthesized in the hope that they would not be attacked so rapidly by cholinesterase. Among these, a few have been found so stable that they can even be given orally.

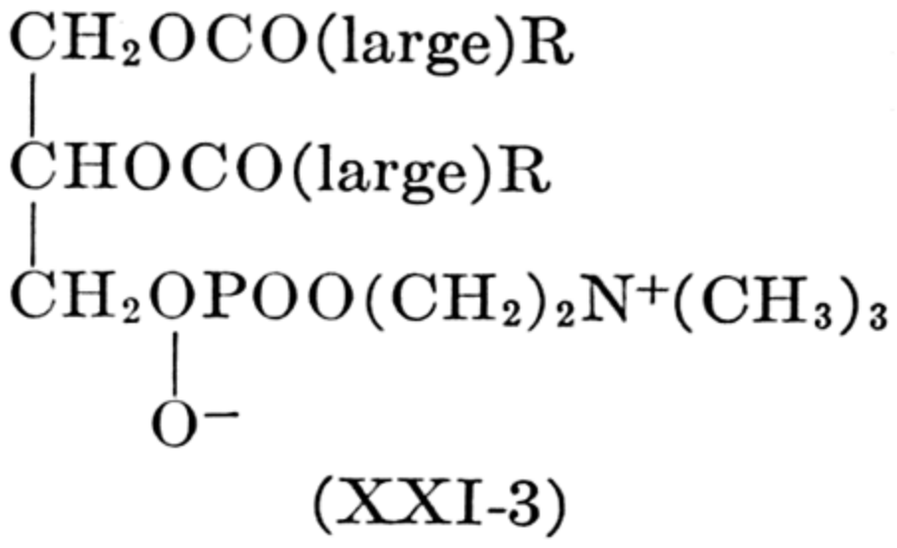
1. Structural Variations

A steady overlapping of the three types of activity of the parent compound of the series, choline, is encountered as one alters the structure of some of its derivatives. It is not easy to predict which of the properties will be brought to the fore by a given structural change.

a. Choline

Choline [$HOCH_2CH_2N^+(CH_3)_3OH^-$] itself is only weakly active pharmacologically, exhibiting barely 0.001 to 0.2% of the manifestations of acetylcholine. Nevertheless, choline shares with other quaternary bases the ability to excite (nicotinic action), and depress (muscarinic action) parasympathetic nerve structures, and to exert, at suitable concentrations, curariform activity expressed mainly by a paralysis of skeletal muscles. The main useful function of choline is found, however, in a different connection. By being incorporated in the lecithins (XXI-3) and being liberated reversibly from them under the influence of the lecithinases, it aids in the transport of fatty acids and fats across hydrophilic media and

[8] Baeyer, *Ann.*, **142,** 322 (1867).



(XXI-3)

membranes. This biochemical function has been utilized in the treatment of hepatic diseases with fatty infiltration; the choline removes fat from the liver and thereby aids in the recovery of the diseased organ.

Esterification of choline to acetylcholine proceeds under the influence of choline acetylase. This enzyme has been extracted from various animal organs. It is a member of an enzyme system which includes adenosine triphosphate (ATP) and phosphocreatine, and shows again the connection of the "acetylcholine cycle" with carbohydrate metabolism.[9]

b. Simple Choline Esters and Their Analogs

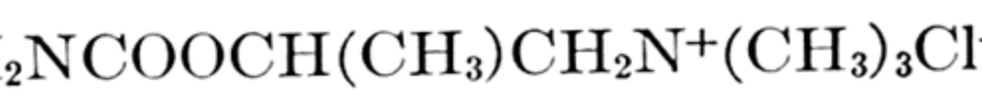
The only analogs of acetylcholine now in clinical use are the halides of acetyl-β-methylcholine (Mecholin, Mecholyl, XXI-4), carbamylcholine (Doryl, Lentin, XXI-5) and Urecholine (XXI-6). They are either not hydrolyzed by cholinesterase or only so slowly that their therapeutic manifestations can be utilized before they are destroyed by the enzyme. It is doubtful whether they exert their activity by competing with acetylcholine for a place on the reactive surface of cholinesterase. This mechanism distinguishes them from the aromatic carbamates, physostigmine and Prostigmin (see below). However, if the effect of acetylcholine is abolished by a parasympatholytic agent (atropine, etc.) these analogs, refractory to enzymatic decomposition, may take the place of the hormone and overcome the action of the blocking agent.



(XXI-4)



(XXI-5)



(XXI-6)

The β-methylcholine (XXI-7) underlying Mecholyl was synthesized by two routes.[10] Chloroacetone and trimethylamine furnished trimethyl-

[9] Nachmansohn, Cox, Coates, and Machado, *J. Neurophysiol.*, **6,** 383 (1948).
[10] Major and Cline, *J. Am. Chem. Soc.*, **54,** 242 (1932).

acetonylammonium chloride (XXI-8) which was reduced over Adams' catalyst. Acetylation with acetic anhydride gave the final drug. The

$$CH_3COCH_2Cl + (CH_3)_3N \rightarrow CH_3COCH_2N^+(CH_3)_3Cl^- \xrightarrow{H_2}$$

(XXI-8)

$$CH_3CHOHCH_2N^+(CH_3)_3Cl^- \xrightarrow{Ac_2O} CH_3CH(OCOCH_3)CH_2N^+(CH_3)_3Cl^-$$

(XXI-7) (XXI-4)

$$\uparrow$$

$$CH_3CHOHCH_2Cl + N(CH_3)_3$$

(XXI-9)

second route used the condensation of propylene chlorohydrin (XXI-9) with trimethylamine, followed by acetylation of the basic alcohol.

Isomers of Mecholyl have also been described in the literature. They are prepared from the corresponding quaternary ammonium alcohols with acetic anhydride. α-Methylcholine was first synthesized by Karrer[11] who obtained its iodide (XXI-10) by the action of methyl iodide on the reduction product (XXI-11) of ethyl N,N-dimethylalaninate (XXI-12).

$$CH_3CH(N(CH_3)_2)COOC_2H_5 \xrightarrow{(H)} CH_3CH(N(CH_3)_2)CH_2OH \xrightarrow{CH_3I} CH_3CH(N^+(CH_3)_3I^-)CH_2OH$$

(XXI-12) (XXI-11) (XXI-10)

The third isomer, γ-homocholine chloride (XXI-13), is obtained from trimethylene chlorohydrine and trimethylamine in benzene solution.

$$ClCH_2CH_2CH_2OH + N(CH_3)_3 \rightarrow Cl^- \cdot (CH_3)_3N^+CH_2CH_2CH_2OH$$

(XXI-13)

Mecholyl has been used in regulating disorders of the heart rate, especially paroxysmal tachycardia, and in patients experiencing spasm of the blood vessels of the extremities when these are exposed to cold, or overagitated in the course of their occupation (Raynaud's disease). Mecholyl can be administered by the customary routes, orally or subcutaneously, but for local application iontophoresis has been found effective in hospitals equipped for this procedure. The active positive ion migrates into the tissues when a pad containing the solution of the drug is placed on the skin under the cathode of a galvanic machine.

Various vascular obstructions (thromboses) are benefited by the vasodilator effects of Mecholyl; specific parasympathomimetic actions of the drug lead to the promotion of intestinal and urinary evacuation.

[11] Karrer, *Helv. Chim. Acta*, **5**, 477 (1922).

Carbamylcholine (Doryl, Lentin) was studied first by Kreitmair.[12] Its aqueous solution is stable on boiling and sterilization. It is said to be more effective than Mecholyl in promoting the evacuation of the colon and the urinary bladder, but Mecholyl is preferred for its action on the heart. Doryl improves muscular tone in myasthenia gravis but Prostigmin (XXI-39) remains the drug of choice in this condition.

Although Doryl is a carbamate like physostigmine or Prostigmin, it does not inhibit the enzyme cholinesterase, and takes the place of acetylcholine by a mechanism similar to that of Mecholyl.

Systematic variations of alkyl radicals in esters of choline have not furnished consistent leads about the relation of the size and kind of such radicals to the pharmacological behavior of cholinergic stimulants. None of the esters of simple, or complex acids approach the powerful action of acetylcholine.[13] Measuring toxicity, and the vasodepressor effect of these compounds, one could generalize that the former increases, and the latter decreases as the structures become less similar to that of acetylcholine. Formylcholine, propionylcholine and butyrylcholine are vasodepressors, but with valerylcholine an irregular series of hypertensive compounds is reached. Esterification of choline with inorganic acids (nitrocholine, $O_2NOCH_2CH_2N^+(CH_3)_3OH^-$, the halogenocholines, $XCH_2CH_2N^+(CH_3)_3$-OH^-) brings about an increase of the muscarinic action of acetylcholine, nitrocholine being the most active inorganic ester.

Alterations of the carbon structure of the aminoalcohol group have to be kept within narrow limits. As shown above for Mecholyl, branching of the carbon chain with a methyl group makes the compound more refractory to enzymatic attack. But if this branching becomes too complicated activity is lost. Introduction of hydroxyl groups or of halogen into the choline structure or the ester groups, or replacement of the aliphatic acyl by aromatic acyl groups, generally reduces the action on blood pressure, and occasionally reverses it. If the aliphatic choline structure is relinquished in favor of heterocyclic quaternary ammonium compounds, curariform activity becomes more pronounced.

Hunt and Renshaw[14] studied ethers of choline, $ROCH_2CH_2N^+(CH_3)_3 \cdot \cdot$-$OH^-$, and thioethers,[15] $RSCH_2CH_2N^+(CH_3)_3 \cdot OH^-$, but most of these compounds exhibited only mediocre curariform activity.[16] In the light of the

[12] Kreitmair, *Arch. exper. Pathol. Pharmakol.*, **164,** 346 (1932).
[13] Fränkel, *Die Arzneimittelsynthese*, 6th Ed. Springer, Berlin, 1927, pp. 336–347.
[14] Hunt and Renshaw, *J. Pharmacol. Exptl. Therap.*, **58,** 140 (1936).
[15] Hunt and Renshaw, *ibid.*, **48,** 105 (1933).
[16] Westphal and Hecht, *Med. u. Chem., Abhandl. med.-chem. Forschungsstätten I. G. Farbenind.*, **3,** 393 (1936).

hypothesis concerning interatomic spacing of muscarinic agents (Sect. V) the failure of these experiments becomes understandable, since the third anchoring group is absent from the ether radicals.

Parasympathomimetic activity is retained if the second oxygen function on the beta-carbon atom is replaced by a vinyl group as shown in Esmodyl (XXI-14). This compound was discovered by the chance observation that the diquaternary salt, Endoiodine (XXI-15)[16] contained an impurity which endowed it with intensive muscarinic activity. The enol ether Esmodyl was identified as the active contaminating agent.

$$CH_2{=}C(OCH_3)CH_2N^+(CH_3)_3\cdot OH^-$$

(XXI-14)

$$I^-(CH_3)_3N^+CH_2CHOHCH_2N^+(CH_3)_3I^-$$

(XXI-15)

Replacement of the alcoholic oxygen atom of choline esters by sulfur does not modify qualitatively the activity of the latter but weakens it (XXI-16).[17] The sulfonium (XXI-17) and phosphonium analogs of acetylcholine (XXI-18) are inferior to acetylcholine in their vasodepressor effects.[18]

$$CH_3COSCH_2CH_2N^+(CH_3)_3\cdot OH^-$$

(XXI-16)

$$CH_3COOCH_2CH_2S^+(CH_3)_3\cdot OH^-$$

(XXI-17)

$$CH_3COOCH_2CH_2P^+(CH_3)_3\cdot OH^-$$

(XXI-18)

An example for a partial reversal of acetylcholine activity is presented by Dibutoline,[19] the dibutyl carbamate of choline chloride, $(n\text{-}C_4H_9)_2NCOOCH_2CH_2N^+(CH_3)_3Cl^-$. This drug exhibits a powerful neurotropic action similar to atropine, that is, it is anticholinergic. The reason for studying this compound was explained by Swan and White.[19] Low-molecular esters of choline are highly hydrophilic but practically insoluble in organic solvents; in other words, they are surface inactive. The introduction of a larger non-polar group into the highly positive ammonium ion was to produce a change in pharmacological behavior. The explanation of the actually observed change, however, remains obscure.

[17] Hunt and Renshaw, *J. Pharmacol. Exptl. Therap.*, **44,** 151 (1932).
[18] Hunt and Renshaw, *ibid.*, **25,** 315 (1925). Prelog, Juhasz, Rezer, and Stern, *Helv. Chim. Acta*, **25,** 907 (1942).
[19] Swan and White, *J. Pharmacol. Exptl. Therap.*, **80,** 285 (1944).

c. Quaternary Ammonium Ions without Ester Function

(1) *Tetraethylammonium Ion*

The quaternary ammonium salts tetraethylammonium chloride or bromide (TEA) would be expected to act like acetylcholine by virtue of the similarity of the "anchoring" group of the two compounds. They are actually found to be cholinergic stimulants as well as blocking agents. TEA can impede both preganglionic sympathetic and parasympathetic nerve impulses at the autonomic ganglia without preceding stimulation. It dilates arteries, and thus decreases blood pressure. The potentiating effect of tetraethylammonium salts on the pressor action of epinephrine has been mentioned in Chapter XIX, and an explanation of this apparently anomalous behavior has been proposed there.

Tetraalkylammonium salts produce curariform paralysis. If the activity of tetramethylammonium halides in this respect is taken as 100, the trimethyl-ethyl salt can be evaluated at 80, dimethyl-diethyl at 8, methyl-triethyl at 2 and tetraethylammonium halide at 0.8. Thus the latter (Etamon) is only very little toxic. As is the case with similar cholinergic materials, atropine effectively counteracts all manifestations of tetraethylammonium ions.[20]

Claims that vasodilation in the limbs resulting from the intravenous injection of tetraethylammonium bromide serves as a reliable prognostic aid in peripheral vascular disease to determine whether a spasm of the vessels is present have not been fully substantiated. However, administration of the drug to patients with essential hypertension has resulted in a considerable fall of blood pressure lasting up to eight hours.[21] In patients suffering from certain types of acute heart failure due to high blood pressure the drug may be used as an emergency treatment. Since tetraethylammonium halide blocks nervous impulses both across sympathetic and parasympathetic ganglia, it can be employed in causalgia (burning pain), a condition caused by post-traumatic degeneration of sympathetic nerve fibers. Here, the drug interrupts the constant bombardment of painful impulses being transmitted to the spinal cord. Other conditions similarly benefited are thrombophlebitis and Buerger's disease,[22] in which alleviation of pain and sometimes sustained improvement results from the administration of the drug. The tetraethylammonium ion may take the place of

[20] Burn and Dale, *J. Pharmacol. Exptl. Therap.*, **6,** 417 (1915). Boyd, Crawshaw, Ratcliffe, and Jepson, *Lancet*, **254,** 15 (1948); Review, *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **9,** 84 (1948).

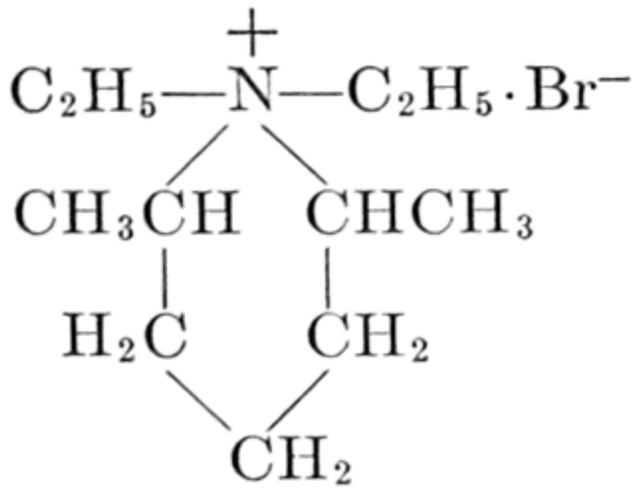
[21] Hayward, *Lancet*, **254,** 18 (1948).

[22] Forsyth, Billard, and More, *North Carolina Med. J.*, **8,** 659 (1947).

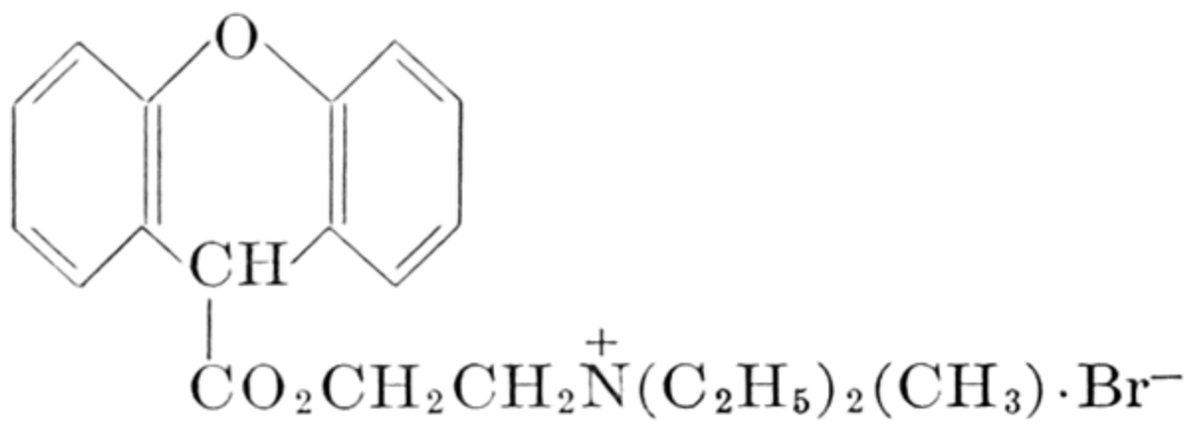
neurosurgical local or paravertebral nerve block in these and similar vascular disorders.[23]

(2) Quaternary Salts in the Treatment of Peptic Ulcers

1,1-Diethyl-2,6-dimethylpiperidinium bromide (XXI-19) inhibits functions mediated by both sympathetic and parasympathetic nerves. It reduces blood pressure and the tonus of the stomach or the small intestine, abolishes their motor activity and reduces gastric acidity.[24] This latter property has been utilized recently in the successful treatment of peptic ulcers, and the dramatic relief of pain caused by such ulcers a few minutes after oral administration of the drug has been reported.



(XXI-19)



(XXI-20)

Similar properties have been reported for Banthine which is orally active in abolishing the activity of the sigmoid colon in man.[24a] The formula of Banthine is represented in XXI-20; it is β-diethylaminoethyl xanthene-9-carboxylate methobromide. The drug is one-half to two-thirds as active as atropine for parasympathetic blockade; it is an effective and well-tolerated anticholinergic drug and has been able to take the place of sympathectomy in patients suffering from hyperhidrosis.[24b]

(3) Quaternary Acetals

Several acetals containing quaternary ammonium groups have been studied for cholinergic properties. γ-Trimethylammonium propanediol acetal (XXI-21 a) and the corresponding formal (Dilvasine, XXI-21 b) pos-

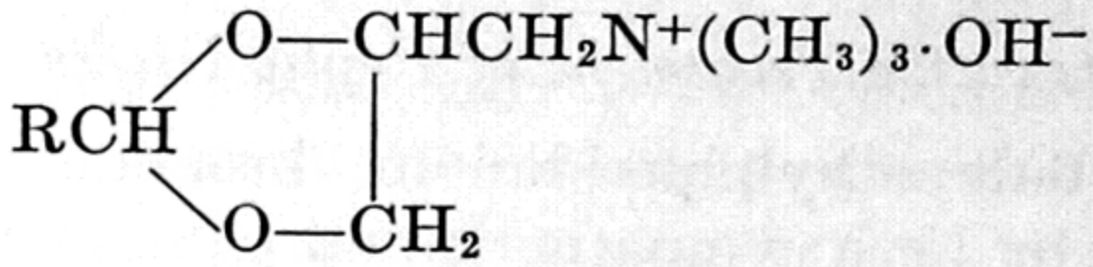
[23] Berry, Campbell, Lyons, Moe and Sutler, *Surgery*, **20,** 525 (1946). Lyons, Moe, Neligh, Hoobler, Campbell, Berry, and Rennick, *Am. J. Med. Sci.*, **213,** 315 (1947).

[24] Longino, Chittum, and Grimson, *Proc. Soc. Exptl. Biol. Med.*, **70,** 467 (1949).

[24a] Kern and Almy, *Am. J. Med.*, **7,** 393 (1950). Cusic and Robinson, *Abstracts*, Meeting Am. Chem. Soc., Philadelphia, April 10, 1950, p. 11K. Longino, Grimson, Chittum, and Metcalf, *Gastroenterology*, **14,** 301 (1950).

[24b] Grimson, Lyons and Reeves, *J. Am. Med. Assoc.*, **143,** 873 (1950); Grimson *et al.*, *ibid.*, **143,** 1331 (1950); Hambourger *et al.*, *J. Pharmacol. Exptl. Therap.*, **99,** 245 (1950).

sess considerable parasympathomimetic properties.[25] A structural similarity to the furan derivatives described below can be seen readily.



(XXI-21)

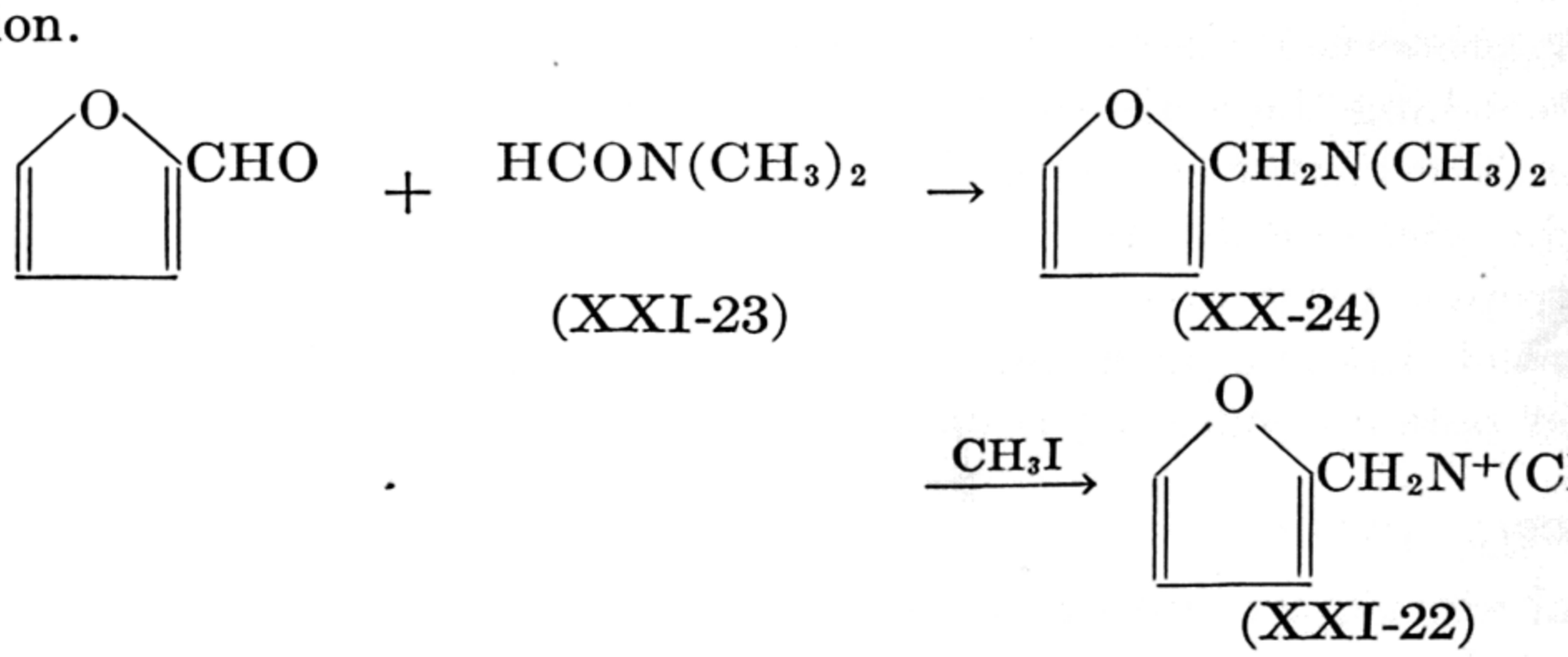
a: R = CH_3

b: R = H

(*4*) *Furmethide*

Of the many other simple quaternary ammonium salts tested, 2-furylmethyltrimethylammonium iodide (Furmethide, XXI-22) has proved useful. Its molecule has about the same distance between the quaternary nitrogen and the heterocyclic oxygen atom that is found in choline, since the two functions are separated by two carbon atoms. The absence of a hydrolyzable ester group contributes towards its stability.

Furmethide is prepared from furfural by a Leuckart reaction with dimethylformamide (XXI-23). The furfuryldimethylamine (XXI-24) from this reaction is converted to the drug with methyl iodide in acetone solution.



(XXI-23) (XX-24)

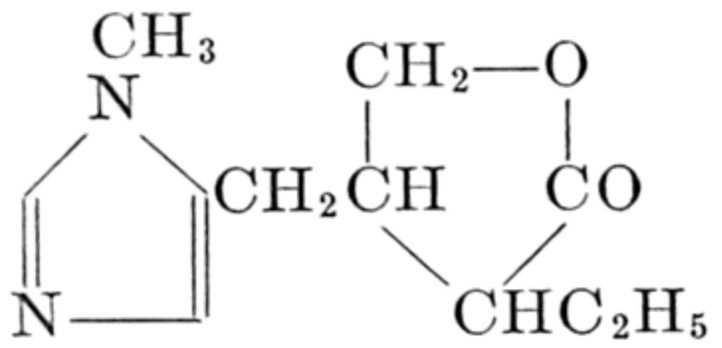
(XXI-22)

Furmethide and similar stable furyl and tetrahydrofurylammonium iodides have been studied by Fellows and Livingston.[26] Although very toxic to dogs, Furmethide is tolerated reasonably well by other species. It lowers blood pressure, causes catharsis, constricts the bronchi, and produces rapid pin-point contraction of the pupil of the eye. The drug has found use in ophthalmology for the reduction of intraocular tension in glaucoma. It improves blood volume in the extremities and can be used to promote evacuation of the bladder and the colon. Its effects are abolished by atropine.

[25] Fourneau, Bovet, Bovet and Montezin, *Bull. soc. chim. biol.*, **26,** 516 (1944).
[26] Fellows and Livingston, *J. Pharmacol. Exptl. Therap.*, **68,** 231 (1940).

II. PILOCARPINE

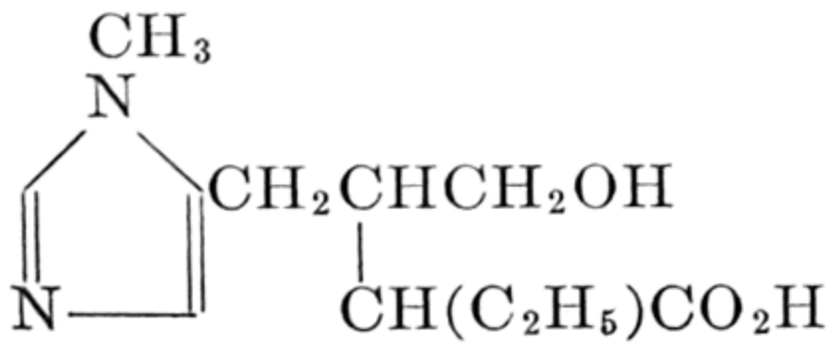
The alkaloid pilocarpine (XXI-25) from the leaves of the South American bush *Pilocarpus jaborandi* is a lactone derived from imidazole. It exhibits parasympathomimetic activity, acting directly on involuntary



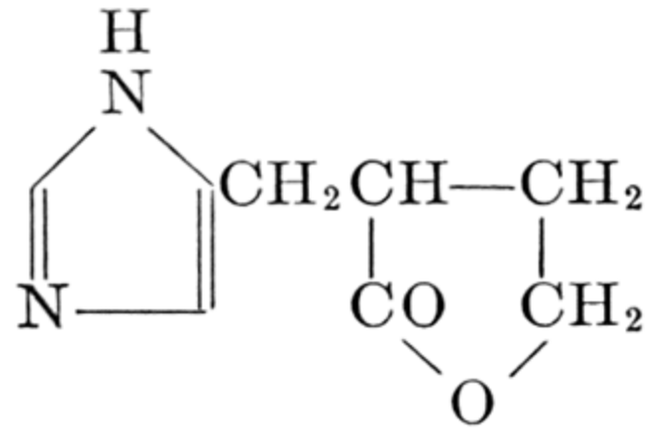
(XXI-25)

muscle and gland cells innervated by postganglionic cholinergic nerves, especially the sweat glands, salivary glands, and gastric glands. It has been used as a diaphoretic (to produce sweating) but this application has been largely abandoned. It is of use in ophthalmology because it produces miosis. Since it stimulates bronchial glands, it has been employed as an expectorant.

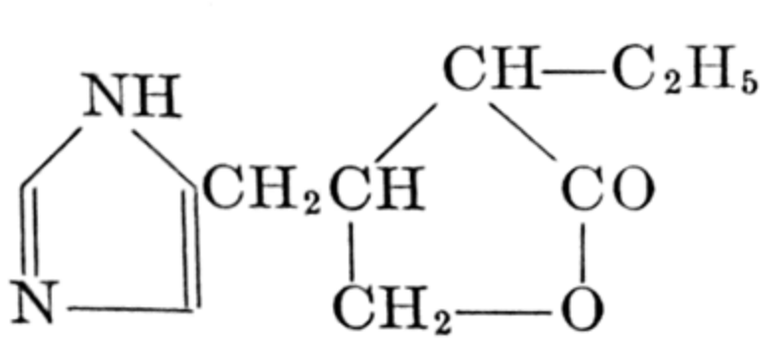
Structural variations diminish, on the whole, the intensity of the cholinergic effects of pilocarpine. Pilocarpic acid (XXI-26) of which pilocarpine is the lactone, is inactive. One might conclude that the lactone function is necessary for activity but this is not the case: α-(5-imidazolylmethyl)-γ-butyrolactone (XXI-27) has no activity either.



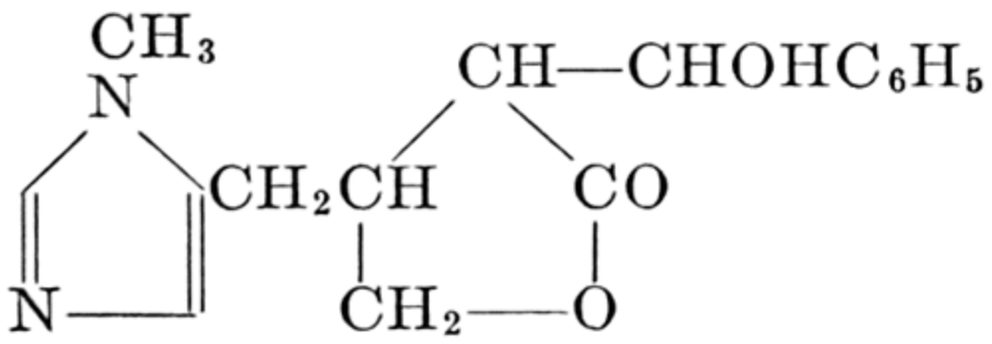
(XXI-26)



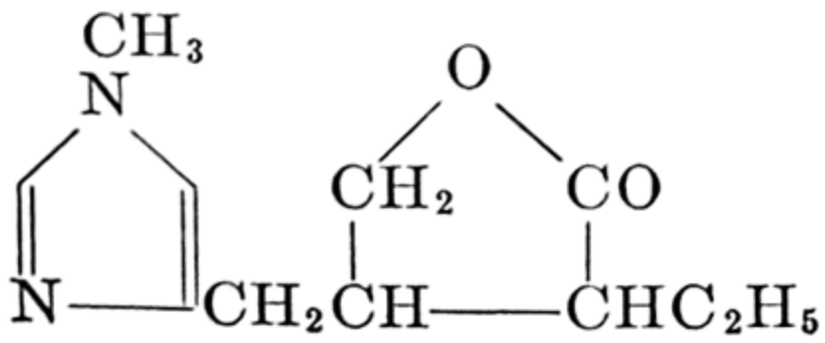
(XXI-27)



(XXI-28)



(XXI-29)

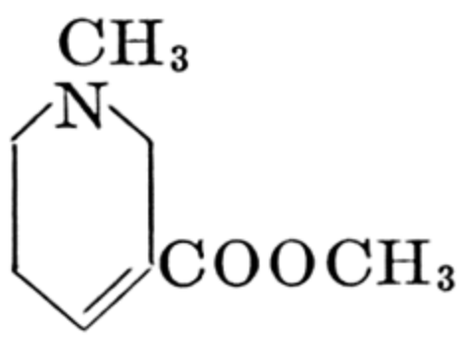


(XXI-30)

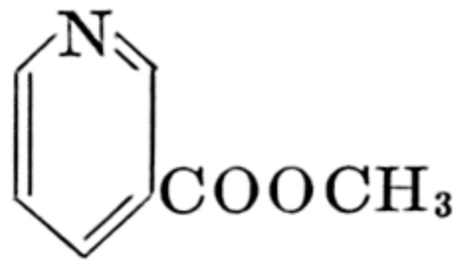
Isopilocarpine, a stereoisomer of pilocarpine, possesses only about one-twentieth the activity of the latter, and pilocarpidine (XXI-28, norpilocarpine), and pilosine (XXI-29), a benzyl alcohol analog, are even less active. A structural isomer of pilocarpine, neopilocarpine (XXI-30) which carries the lactone group in position-4 of the imidazole ring, is completely inactive.[27]

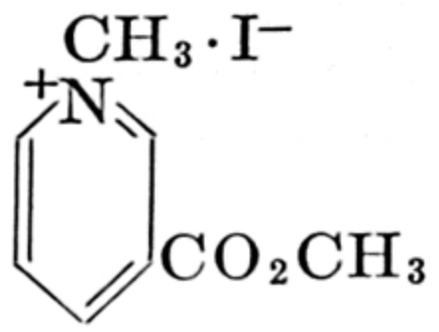
III. ARECOLINE

The areca nuts, the seeds of *Areca catechu*, contain the alkaloid arecoline (methyl 1,2,5,6-tetrahydro-1-methylnicotinate, XXI-31). It is hypotensive and produces typical muscarinic effects. As part of the betel mixture, it has been used as a deworming agent in the Orient for centuries. Arecoline owes its taenicidal (anthelmintic) properties to its cholinergic stimulation of peristalsis by which intestinal parasitic worms are probably expelled. Its use as an anthelmintic is now restricted to veterinary medicine.

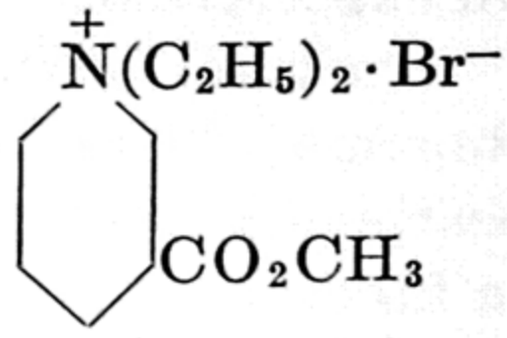


(XXI-31)





(XXI-32)



(XXI-33)

Methyl nicotinate is not a parasympathomimetic stimulant, but its quaternary methiodide (Cesol, XXI-32) as well as the hexahydro derivative Neocesol (XXI-33) are similar to arecoline.[28]

IV. INHIBITORS OF CHOLINESTERASE[29]

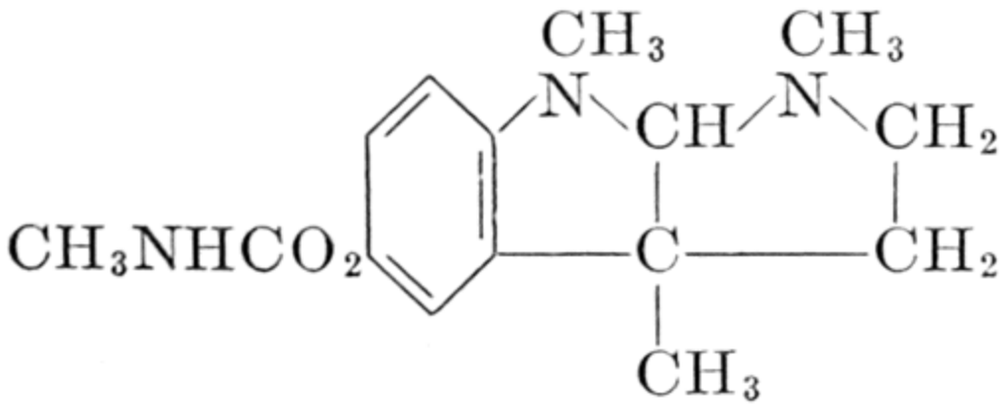
1. Physostigmine

Physostigmine (eserine) is the main alkaloid of the Calabar bean, the dried seed of the African vine *Physostigma venerosum*. The Calabar bean causes toxic symptoms including nausea, vomiting, diarrhea, sweating, salivation, twitching of muscles, pin-point constriction of the pupils and respiratory paralysis leading to death. The initial vomiting produced by an emetic substance in the seed hull may be so violent as to protect the person from fatal amounts of the alkaloid by automatic removal of the beans. On this phenomenon was based their use as ordeal beans in native

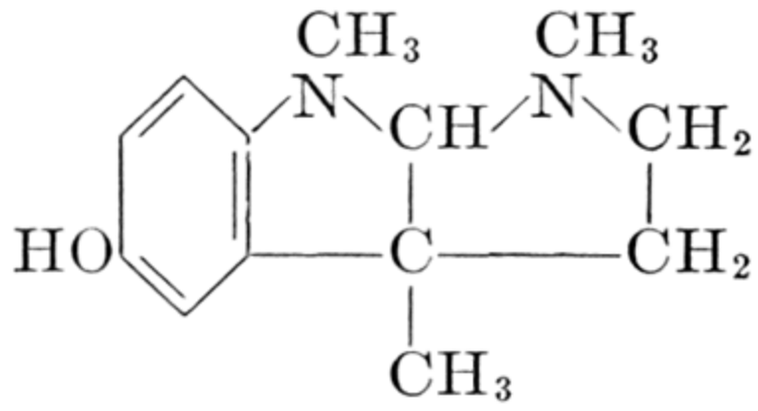
[27] Burtles, Pyman, and Roylance, *J. Chem. Soc.*, **127,** 581 (1925).
[28] Hunt and Renshaw, *J. Pharmacol. Exptl. Therap.*, **35,** 75 (1929).
[29] For a recent review, see Gilman, *J. Pharmacol. Exptl. Therap.*, **95,** 166 (1949).

West African trials. An accused person, if innocent, might swallow the poisonous beans quickly and thus protect himself from absorption while a guilty tribesman, afraid of the ordeal, would eat hesitantly and exhibit the "condemning" symptoms of the toxicity syndrome.

Physostigmine (XXI-34) was isolated in 1864[30] and its structure proved by Barger and Stedman.[31] A synthesis of physostigmine has been published by Julian and Pikl.[32] The alkaloid is the methyl carbamate of physostigmol (eseroline, XXI-35). This carbamate structure not otherwise encountered in alkaloid chemistry, has been the clue to the understanding of the pharmacological behavior of the compound and has been imitated in synthetic analogs, especially Prostigmin and its congeners.



(XXI-34)



(XXI-35)

Physostigmine prevents the enzyme cholinesterase from catalyzing, in its accustomed manner, the hydrolysis of acetylcholine. It is assumed that physostigmine competes with acetylcholine for a reactive place on the enzyme; the carbamate group preoccupies the hydrolytic ability of cholinesterase, while acetylcholine remains unsaponified and acquires time to exert all its ordinarily short effects. As a result, physostigmine protects the hydrolytic destruction of acetylcholine in all cholinergic locations in the body, in parasympathetic as well as sympathetic ganglia, and at the junctures of cholinergic nerves with glands or muscles. This explains the often contradictory behavior of the organism after administration of physostigmine. The blood pressure may be lowered, as acetylcholine begins to act uninterruptedly at cholinergic nerve endings, or raised when acetylcholine is not hydrolyzed in sympathetic ganglia. The adrenal medulla will be stimulated unduly by the continuous availability of acetylcholine and thus produce more Adrenalin which, in turn, will antagonize some of the effects of physostigmine.

Further proof for the proposed mechanism of action of physostigmine can be obtained by obliterating the substrate of cholinesterase, acetylcholine, by surgical destruction of a cholinergic nerve. If, for instance,

[30] Jobst and Hesse, *Ann.*, **129,** 115 (1864); **141,** 913 (1867).
[31] Barger and Stedman, *J. Chem. Soc.*, **119,** 891 (1919); **123,** 759 (1923).
[32] Julian and Pikl, *J. Am. Chem. Soc.*, **57,** 539, 755 (1935).

the nerves to the iris of the eye are cut, physostigmine will no longer cause contraction. It still inhibits cholinesterase, but no acetylcholine is preserved from destruction, and the iris has no reason to respond to the alkaloid.

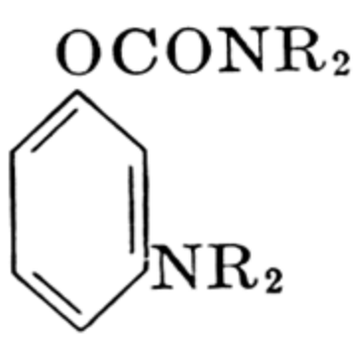
The parent phenol of physostigmine, physostigmol (XXI-35) is almost inactive as an inhibitor of cholinesterase.

Physostigmine has been used as a peristaltic, but has given way very largely to Prostigmin for the same therapeutic uses, not because of a more favorable therapeutic index of the latter, but because some of the undesirable side effects of acetylcholine, especially those on the heart, are less noticeable when Prostigmin is employed. The instability of the alkaloid has also played a role in relegating physostigmine to a secondary place; solutions of its salt decompose on standing. It is still used in ophthalmology to reduce intraocular pressure in glaucoma, and to cause miosis (contraction of the pupil), especially after atropinization. There is no question, however, that Prostigmin is more effective in the most striking condition benefited by inhibitors of cholinesterase, myasthenia gravis.

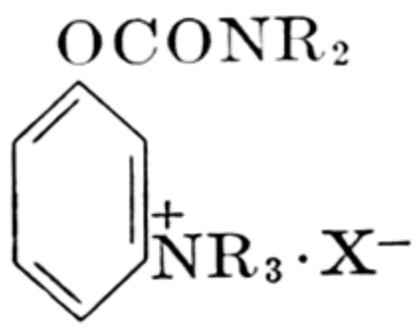
2. Prostigmin

The easily hydrolyzable urethan group of physostigmine, and the disappearance of anti-cholinesterase activity in physostigmol, have centered attention upon systematic structural variations of aromatic carbamates ($ArOCONR_2$).

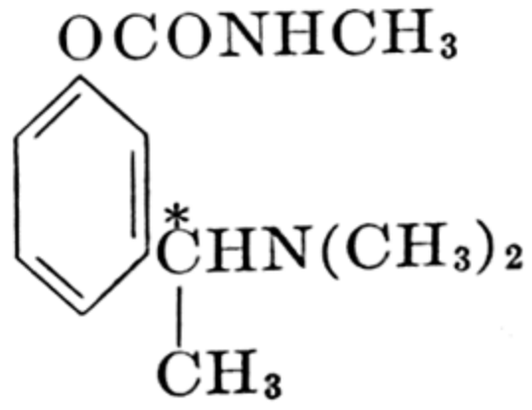
It would have been natural to expect some connection between *p*-aminophenylurethans and physostigmine since the pyrroline nitrogen of the alkaloid occupies that position relative to the carbamate radical. However, a series of alkyl carbamates of basically substituted phenols, tested as miotics, produced highest activity values for *m*-derivatives. It was also found[33] that several of the quaternary ammonium salts (XXI-36) were more active than the tertiary amines (XXI-37), perhaps because the aminophenols are weak bases and give salts with a strongly acid reaction. Following up this lead, White and Stedman removed the basic tertiary



(XXI-37)



(XXI-36)



(XXI-38)

[33] Stedman, *Biochem. J.*, **20,** 719 (1926); **23,** 17 (1929). Stedman and Stedman, *J. Chem. Soc.*, 609 (1929).

amino group into a side-chain and introduced one of these more basic compounds (XXI-38) under the name of Miotine.[34] The levorotatory isomer of this drug was the more active of the two enantiomorphs. One of the main reasons why this compound could not retain its place among therapeutics was again the instability of its aqueous solutions; even water alone hydrolyzes it fairly soon to the physiologically inert parent phenol. The quaternary salt of compound (XXI-38) did not show higher activity. Apparently, when the basic radical is in a side chain rather than directly attached to the aromatic nucleus, differences in activity are less marked; in some cases, they may even be reversed.

A re-investigation of some of Stedman's and similar compounds as miotics and peristaltics revealed that the *m*-dialkylaminophenyl carbamate structure is necessary (m-$R_2NC_6H_4OCONR'_2$) for activity.[35] If one of these groups is omitted the compound becomes inactive. This holds also for another important activity, the relaxation of muscles paralyzed by curare. The effect of altering substituents at the carbamate nitrogen is tabulated below.

TABLE I. PHYSOSTIGMINE ACTIVITY OF *m*-DIALKYLAMINOPHENYL URETHANS

m-$R_2NC_6H_4OCON\begin{matrix}R'\\R''\end{matrix}$		Physostigmine activity
R′	R″	
$-CH_3$	CH_3	++
$-CH_3$	H	++
$CH_2{=}CHCH_2-$	H	++
$-CH_2C_6H_5$	H	++
$-C_6H_4CH_3$	H	++
$-C_2H_5$	H	+
$-C_6H_5$	H	+
$-C_2H_5$	$-C_2H_5$	0
$-CH_2CH{=}CH_2$	$-CH_2CH{=}CH_2$	0

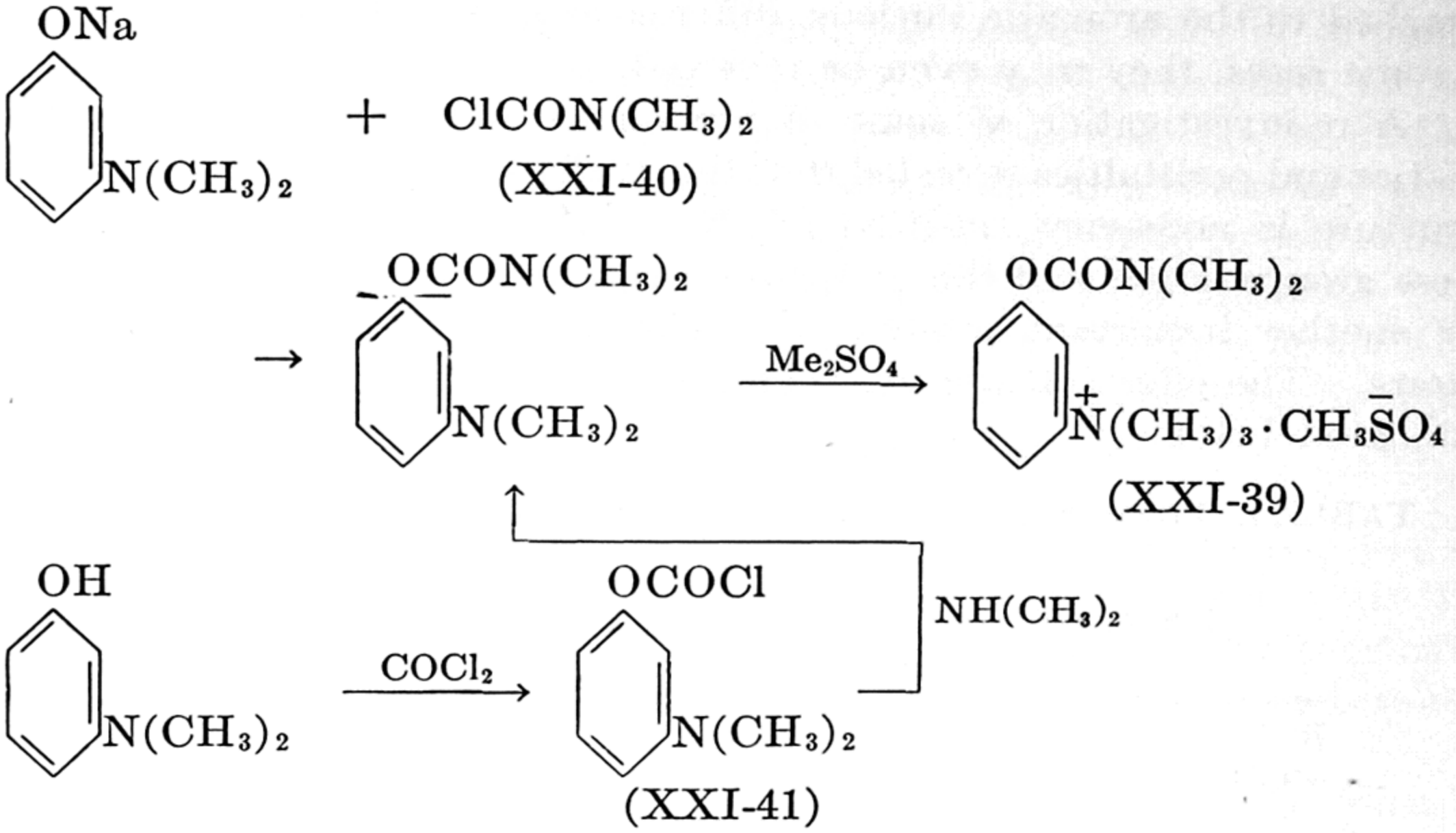
The quaternary methosulfate of *m*-dimethylaminophenyl dimethyl carbamate (XXI-39) was singled out as the most suitable drug in this series. Under the name of Prostigmin (formerly Neostigmine) it has virtually replaced physostigmine in therapeutic applications requiring inhibi-

[34] White and Stedman, *J. Pharmacol. Exptl. Therap.*, **41,** 259 (1931).

[35] Aeschlimann and Reinert, *J. Pharmacol. Exptl. Therap.*, **43,** 413 (1931). Aeschlimann, *J. Soc. Chem. Ind.*, **54,** 135T (1935). Aeschlimann and Stempel, *Jubilee Volume Emil Barell,* Reinhardt, Basle, 1946, p. 306.

tion of cholinesterase. Its solution is not hydrolyzed if buffered at pH 3 to 4.

Prostigmin may be synthesized by two routes. Sodium *m*-dimethylaminophenolate can be treated with N,N-dimethyl chlorocarbonate (XXI-40), or *m*-dimethylaminophenyl chlorocarbonate (XXI-41) obtained from the phenol and phosgene, can be aminated with dimethylamine. The tertiary aromatic amine obtained from either reaction is then quaternized with methyl sulfate.



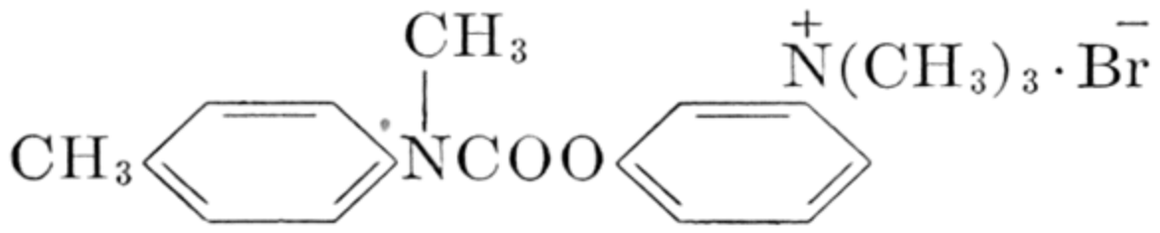
Prostigmin causes miosis but is seldom employed for this purpose. It is useful in the control of distension of the bowel or urinary bladder and finds wide use in post-operative suffering from intestinal gases. The most striking benefit derived from the drug is in myasthenia gravis. This is a spastic condition of skeletal muscle, a muscular atony which prevents the patient from moving his extremities, and from talking and swallowing. A person afflicted with this disease presents a picture not unlike one paralyzed by curare. Since physostigmine and Prostigmin were known to counteract this paralysis, these drugs were tried in myasthenia gravis,[36] and Prostigmin proved to be superior to the natural alkaloid. Within a few minutes, bed-ridden paralyzed patients can walk, talk and swallow and will retain normal abilities until the effect of the drug wears off, and a new dose must bring relief.

Other conditions accompanied by skeletal muscle spasm in which Prostigmin has been found to improve muscle tone are the after-effects of

[36] Walker, *Proc. Roy. Soc. Med.*, **28,** 759 (1935).

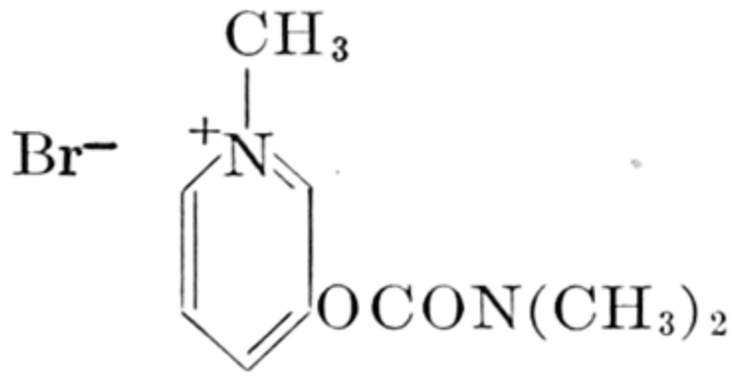
poliomyelitis and rheumatoid arthritis.[37] It is interesting that in these conditions the effect on the transmission of impulses from nerves to muscles of Prostigmin resembles that of curare, instead of being antagonistic to it. A pharmacological explanation of this phenomenon has not yet been found but some satisfaction may be derived from the fact that salts of curarine are quaternary ammonium salts, that all other quaternary onium salts have curare-like activity, and that Prostigmin may owe this property to its own quaternary nature. A number of analogs of Prostigmin having the two important functions, the urethan and quaternary salt groups, ortho to each other, exhibit this curare-like behavior even to a greater extent. However, their cholinesterase-inhibiting power decreases as their curare-like action grows.

The anticurare properties of Prostigmin must thus be attributed to the non-quaternary, hydrolyzable urethan group which is the decisive factor in its inhibition of cholinesterase. That there is an overlapping of



(XXI-42)

curariform and anticurare properties is shown by the N-methyl-toluidino urethan (XXI-42) which inhibits cholinesterase more strongly than physostigmine, and has curare-like properties.[38] On the other hand, the de-



(XXI-42a)

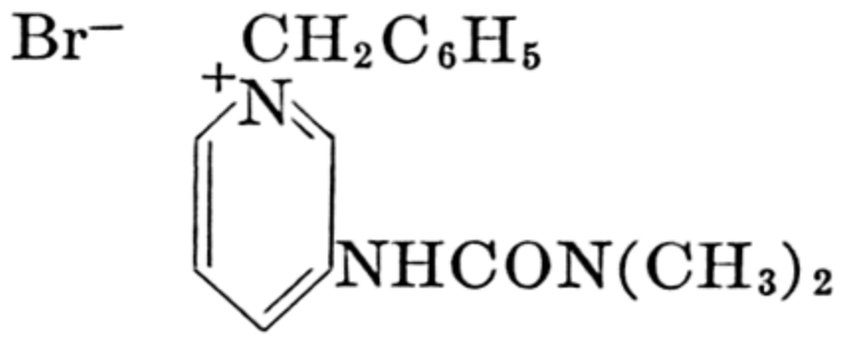
curarizing effect of the pyridine analog (XXI-42 a) is quite independent of its inhibitory effect upon cholinesterases.[38a]

3. Other Urethans

Among fifty quaternary pyridinium salts carrying urethan groups in the 3-position, 1-benzyl-3-(dimethylcarbamyloxy) pyridinium bromide (Stigminene, XXI-43) was the most potent drug. It stimulated peristalsis

[37] Lehmann, *Jubilee Volume Emil Barell*, Reinhardt, Basle, 1946, p. 314.
[38] Aeschlimann, U. S. Pat. 2,449,440 (1948).
[38a] Casier and Verbeke, *Arch. internat. pharmacodyn. therap.*, **83,** 452 (1950).

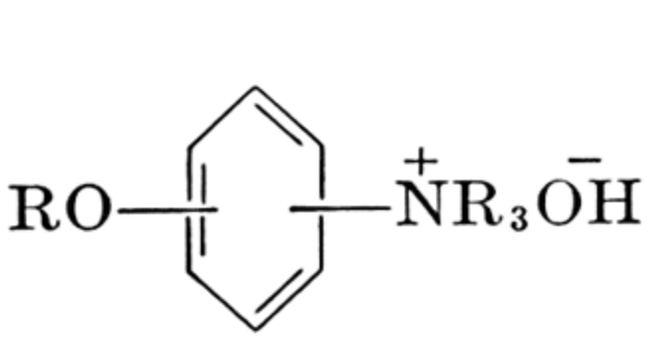
in doses of 0.1 mg./kg. and inhibited cholinesterase *in vitro* at a concentration of 3×10^{-9} mole per milliliter.[39]



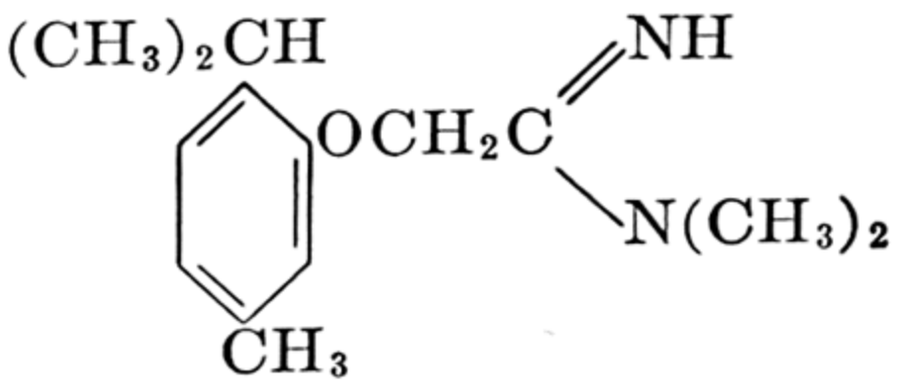
(XXI-43)

A significant side light is thrown on the whole group of aromatic urethans by a patent claiming their usefulness as bait poisons.[40] This underscores the high toxicity of these compounds, and also reemphasizes the necessity of explaining toxic manifestations in any series of drugs on the basis of inhibition of important enzyme systems. Morphine, strychnine curare and methylene blue are known to be inhibitors of cholinesterase,[41] and others will probably be added to this series. The toxicity symptoms evoked by so many drugs, especially nausea, vomiting, dizziness, salivation, intestinal spasms etc. are so similar for many apparently unrelated compounds that a common basis of their origin should be sought. It would not be surprising to find that *in vitro* and *in vivo* studies of enzyme inhibition by these drugs can give the answer to this problem.

In analogy to other quaternary ammonium salts, alkoxy substituted aryl trialkylammonium ions (XXI-44) have been found to have Prostigmin-like properties.[42] Anticholinesterase activity has also been found to reside in certain substituted aryloxyamidine derivatives. Thus, N,N-dimethylthymoloxyacetamidine (XXI-45) possesses both oral and topical activity.[43] The diiodomethylate of bis-(*p*-dimethylaminophenoxy)-1,3-propane, $[I^- \cdot (CH_3)_3N^+\text{-}p\text{-}C_6H_4OCH_2]_2CH_2$, is as potent an anticurare agent as Prostigmin and is said to have a more favorable therapeutic index.[43a]



(XXI-44)



(XXI-45)

[39] Wuest and Sakal, *Abstracts*, 115th Meeting, Am. Chem. Soc., San Francisco, Cal., March 1949, p. 7K.

[40] Aeschlimann, U. S. Pat. 1,858,177 (1932).

[41] Bernheim, *The Interaction of Drugs and Cell Catalysts*. Burgess, Minneapolis, 1942.

[42] Gardner and Stevens, *J. Am. Chem. Soc.*, **59,** 3086 (1947).

[43] Djerassi and Scholz, U. S. Pat. 2,425,730 (1947).

[43a] Funke and Depierre, *Compt. rend.*, **230,** 245 (1950).

4. Diisopropyl Fluorophosphate (*DFP*)

In the course of war-time research on toxic gases, the observation of Lange and Krueger[44] was remembered, that the vapors of dialkyl fluorophosphates, $(RO)_2P(O)F$, cause visual and respiratory impairment at low concentrations. When esters of this type were reexamined, the chemists McCombie and Saunders[45] noticed that the cyclohexyl, isopropyl, sec.-butyl and other derivatives had a miotic action on the eye. The compounds were then tested as miotics,[46] and the most potent member of the group, diisopropyl fluorophosphate (*DFP*, $[(CH_3)_2CHO]_2P(O)F$) was singled out as the most promising drug for further study. It turned out to be the most powerful inhibitor of cholinesterase yet discovered.

The margin of safety of *DFP* is narrow, and it is unlikely that this toxic agent will become an important therapeutic agent although Parpanit and Diparcol can completely antagonize its effects. However, *DFP* has become an interesting pharmacological tool. It inactivates cholinesterase reversibly after short exposures, and irreversibly after prolonged action on the enzyme at a concentration of 10^{-11} mole. One can utilize this biochemical behavior to substantiate some hypotheses implicating cholinesterase as a causative pathogenic factor. If, for instance complete inhibition of cholinesterase were the answer to healing myasthenia gravis, *DFP* should prove valuable in this condition. Yet, it exhibits only slight activity.[47]

Another experiment with *DFP* has changed our view concerning the mode of action of physostigmine and Prostigmin. As pointed out above, these urethans are regarded as inhibitors of cholinesterase, that is, they preserve acetylcholine from hydrolysis by this enzyme. If the enzyme has been completely and irreversibly poisoned by *DFP*, the urethans should no longer be able to serve as substrates, and consequently become inactive. Actually, they retain cholinergic effects under these conditions. This has led to the suggestion that the action of Prostigmin on muscle or gland cells is similar to that of a true choline ester.[48]

Apart from alterations of the alkyl radicals, the effects of other structural changes on the anti-cholinesterase activity of *DFP* have also been studied. The thioester $(C_2H_5S)_2POF$ is inactive, and so is ethyl difluorophosphate $((C_2H_5O)POF_2)$. In esters of the type $(C_2H_5O)_2POX$ in which

[44] Lange and Krueger, *Ber.*, **65,** 1598 (1932).
[45] McCombie and Saunders, *Nature*, **157,** 287 (1946). Saunders, *Chemistry and Industry*, **1947,** 117.
[46] Adrian, *Nature*, **158,** 625 (1946).
[47] Comroe, Todd, Gammon, Koelle, and Gilman, *Federation Proc.*, **5,** 172 (1946). Harvey, Jones, Talbot, and Grob, *ibid.*, **5,** 182 (1946).
[48] Riker and Wescoe, *J. Pharmacol. Exptl. Therap.*, **88,** 58 (1946).

a variety of groups can take the place of the fluorine atom, toxicity is negligible. Variations of effects were studied by measuring miotic activity, that is, reduction of intraocular pressure provoked by cholinergic stimulation.[49]

5. Phosphate Insecticides

Recent studies of the intensely toxic insecticides, tetraethyl pyrophosphate [*TEPP*, $(C_2H_5O)_2P(O)OP(O)(OC_2H_5)_2$] and diethyl *p*-nitrophenyl thiophosphate [Parathione, $(C_2H_5O)_2PS(p\text{-}OC_6H_4NO_2)$] have revealed that these compounds are powerful inhibitors of cholinesterase. Their toxic effects in mammals are cancelled out by atropine. *TEPP* has been tested as a therapeutic agent in myasthenia gravis, but its margin of safety is too small for use in medicine.[50]

Octamethyl pyrophosphoramide, $[(CH_3)_2N]_2P(O)OP(O)[N(CH_3)_2]_2$, has recently been found to inhibit predominantly peripheral cholinesterase without exerting any effects on the central nervous system.[51]

V. RELATION OF MUSCARINIC ACTION TO SPATIAL GROUPINGS

There has been a changing tendency over the years to regard a given portion of a molecule, or the whole molecule of a drug, as responsible for the pharmacological behavior of the compound. The view held most widely twenty years ago that hydroxyl groups have depressant, amino groups excitant, and other functional groups corresponding other activities has been completely abandoned. It was followed by a period in which the innumerable exceptions to every postulate of structure-action relation discouraged chemists from pinning definite physiological functions on specific groups. The idea began to gain ground that predictions were unfeasible, and each molecule as a whole acted in its own peculiar way. This preference was supported by advocates of steric considerations who called attention to the possibility that the molecule of a drug might fill an open space on the surface of an enzyme and thereby divert certain reactions normally catalyzed by this enzyme. Any drug, regardless of its fine structure, which would have a shape suitable to fill the same space (which would be "isosteric") could fulfill the same blocking function on the active surface.

Recently, this view has been re-interpreted to mean that certain selected groups of atoms within the molecule of a drug are the actual units which must fit into reactive spots or indentations of the active surface of

[49] McCombie and Saunders, *Nature*, **157,** 776 (1946); **158,** 382 (1946).
[50] Grob and Harvey, *Bull. Johns Hopkins Hosp.*, **84,** 533 (1949).
[51] DuBois, Doull, and Coon, *Abstracts*, Indianapolis Meeting, Am. Soc. Pharmacol. Exp. Therap. Nov. 17, 1949, p. 20.

the proteinogenous enzyme. It will be necessary in most cases to have at least three "prosthetic groups" in the drug molecule to fit the latter firmly into the proper spaces of the enzyme, or as some authors still prefer to call it, the receptor on the cellular surface. A, B and C in Figure 1 represent such prosthetic atoms or groups which fill, by virtue of their sterical configuration, corresponding spaces in the molecule of an enzyme. As Clark[52] has put it, pharmacological action in many instances depends on the activation or deactivation of receptors on the cellular surface by specific chemical groups of the drug molecule.

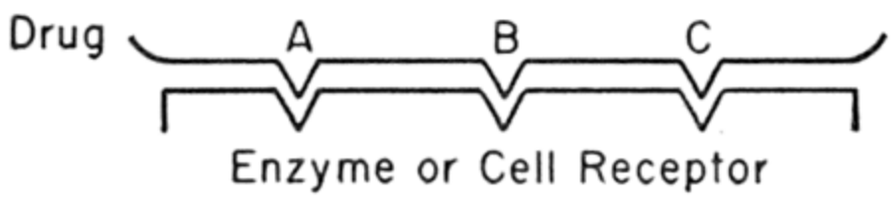


Figure 1. Schematic Drawing of "3-Point" Fitting

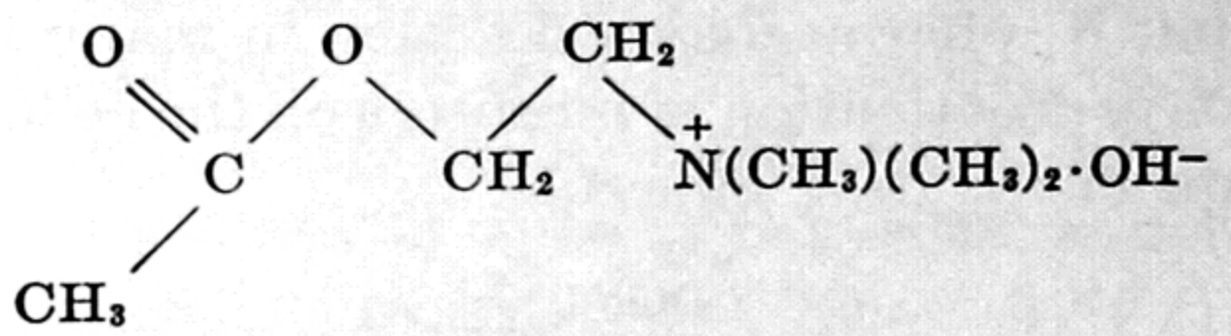
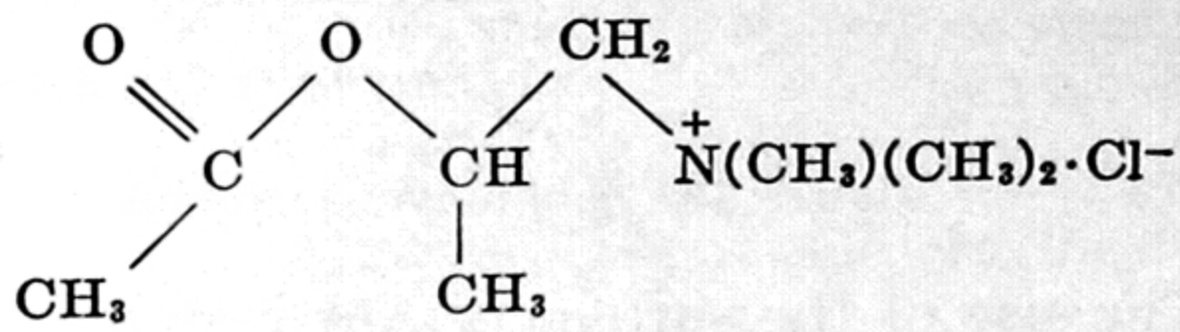
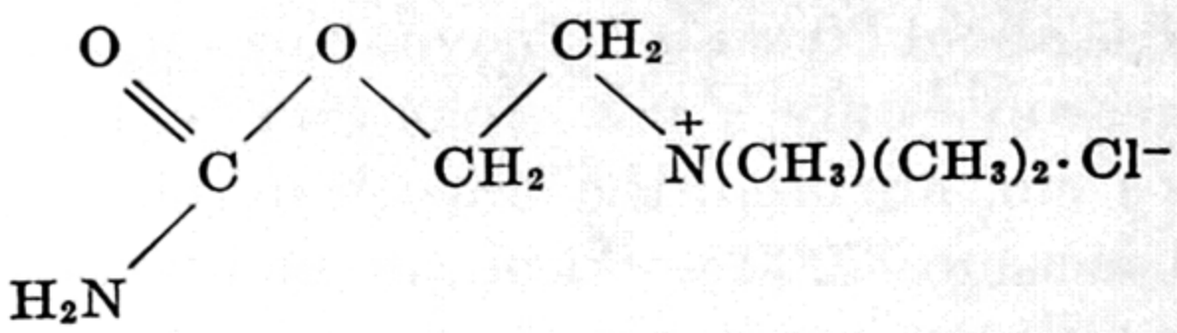
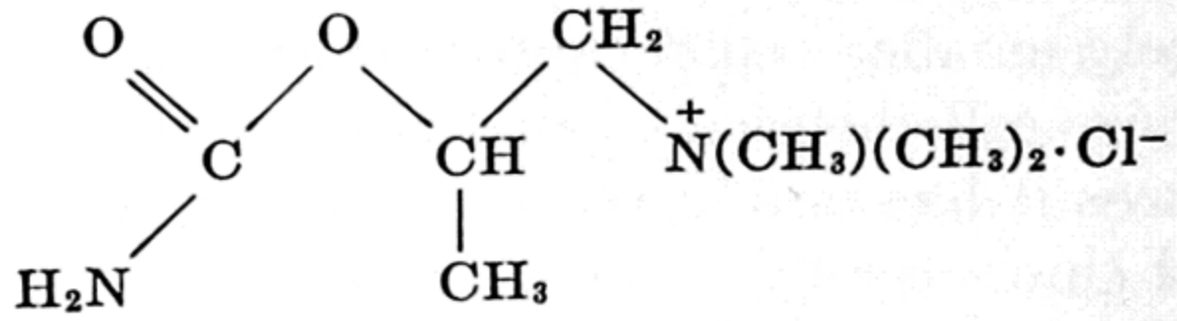
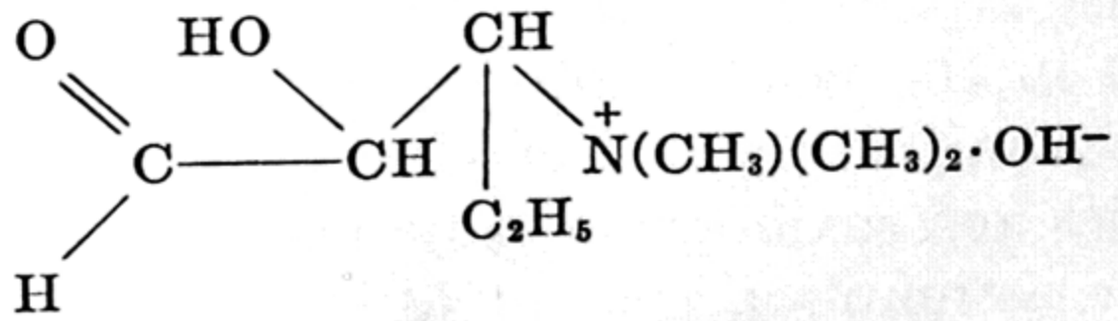
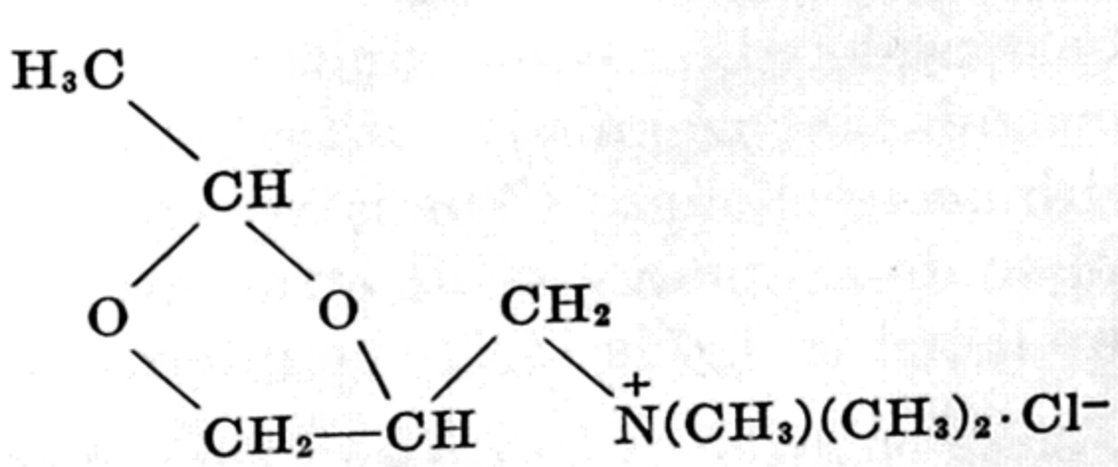
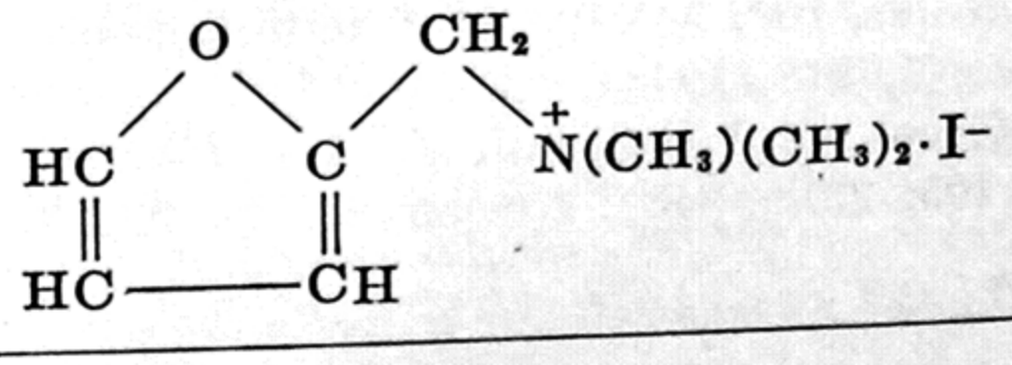
The size of the surface of, for instance, the cell of a vascular smooth muscle is about 20 x 1 μ. In comparison, the molecule of a drug of average size measures only a few Ångström units. If atomic models where 1 Å equals 1 cm. are used, the smooth muscle cell, if drawn to the same scale, would measure 2000 x 100 m., or be about 1.25 miles long and the length of two railroad coaches in diameter. We are therefore concerned with the infinitely smaller cell receptors themselves, which are usually regarded as small size cell chemicals, or at best as cell proteins or enzymes. In several instances it has now become possible to correlate drugs of a given physiological character by comparing the interatomic distances of some of their prosthetic groups which fit into, or react with active locations of the same distance in the cell receptors. This has been done especially successfully for muscarinic drugs and cholinergic blocking agents by Pfeiffer,[53] and for analgetics and sex hormones by Schueler.[54]

The assumption that at least three significant interatomic distances should be considered for compounds exhibiting muscarinic activity is based on the insignificant magnitude of the stimulating action of choline as compared with acetylcholine. The latter contains one more oxygenated function, and so do a number of its structural and pharmacodynamic analogs which are listed in Table II. The interatomic distances for acetylcholine,

[52] Clark, *Mode of Action of Drugs on Cells*. Arnold, London, 1933.
[53] Pfeiffer, *Science*, **107,** 94 (1948). Pfeiffer, Santos–Martinez, and Sherrod, *Federation Proc.*, **7,** 248 (1948).
[54] Schueler, Gross, and Holland, *J. Am. Pharm. Assoc.*, **38,** 74 (1949). Schueler, *Science*, **103,** 221 (1946); *Endocrinology*, **38,** 401 (1946).

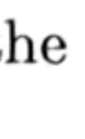
as determined from atomic scale models, are 7.0 Å from carbonyl oxygen to the center of methyl (N^+CH_3), and 5.3 Å from ether oxygen to the same methyl group. These distances must be the same for Mecholyl, Doryl and Urecholine. The formula given for muscarine (XXI-1) has about the same

TABLE II

Acetylcholine (XXI-2)	
Mecholyl (XXI-4)	
Doryl (XXI-5)	
Urecholine (XXI-6)	
Muscarine[6] (XXI-1)	
2, 3-Propanediol-acetal-trimethylammonium chloride[55] (XXI-20)	
Furmethide (XXI-22)	

[55] Fourneau, Bovet, Bovet, and Montezin, *Bull. soc. chim. biol.*, **26**, 134, 516 (1944).

interatomic distances (5 Å and 6.7 Å, respectively) as does acetylcholine, and is therefore preferable to the older, and not yet disproved formula, $OCHCHN^{+}(CH_3)_3 \cdot OH^{-}$. The acetal (XXI-20) does not contain a car-



$HOCHC_2H_5$

bonyl oxygen but another acetal oxygen atom. The distances between these two oxygen atoms and the N-methyl group are 5 Å, and 7.0 Å, that is, close to the optimum for muscarinic action. The compound acts in a dose of 1 γ/kg. and demonstrates that the cell enzymes do not distinguish between ether, acetal or carbonyl oxygen atoms provided they are properly spaced.

In Furmethide, the heterocyclic resonating double bond between C_4 and C_5 seems to take the place of the C=O linkage. It may be significant that Furmethide was chosen as the best therapeutic agent from a series of similar drugs, especially tetrahydrofuryl derivatives. Seen in the light of the atomic spacing hypothesis, the aromatic heterocyclic nucleus may be the cause of its greater analogy to acetylcholine.

Similar models can be constructed for the cholinergic stimulants, arecoline, pilocarpine, physostigmine and Prostigmin; the latter acts, at least in part, as a parasympathomimetic drug although it owes most of its action to its inhibition of cholinesterase. In a model of Prostigmin the magnitude of the distances from ether oxygen to NCH_3 (7.0 Å), and carbonyl oxygen to NCH_3 (8.5 Å) is reversed, a further indication that the chemical function of the oxygen atoms is immaterial for muscarinic action. These thoughts will also be reverted to later for curariform compounds, and inhibitors of acetylcholine stimulation.

Ing[56] has criticized Pfeiffer's hypothesis on the basis that not all compounds containing the three "prosthetic groups"—they should be called pharmacodynamic groups to distinguish them from active molecules attached to high-molecular carriers—show parasympathomimetic activity, but some compounds which show such actions do not contain all three groups. There is an enormous quantitative difference between esters of choline with various simple acids, and between acetylcholine. More complex choline esters often have nicotinic and, occasionally, even anticholinergic properties (cf. Dibutoline). Simple alkyl ethers of choline have clearly muscarinic activity, and this holds also for alkyltrimethylammonium salts; both classes of compounds lack at least the carbonyl oxygen. On the other hand, the size of the "cationic head" of the molecule is undoubtedly significant since trimethylammonium ions in choline-type compounds are so far superior as parasympathetic stimulants to any compounds having other groups on nitrogen. Likewise, the 5-carbon interval between nitro-

[56] Ing, *Science*, **109,** 264 (1949).

gen atoms pointed out by Pfeiffer is undeniably an important sterical feature for muscarinic action.

Both Pfeiffer and Ing take a static view of nicotinic action in focussing attention on the "receptor spots" or "prosthetic groups" which are the anchoring position of the O—C—C—N systems of cholinergic drugs. A recent discussion of these arguments by Barnes and Beutner[57] points to the dynamic possibilities of explaining cholinergic phenomena. Cholinergic drugs have strong phase–boundary potentials at the interface between saline and lipids; acetylcholine produces a negative phase–boundary potential which can be calculated from the increase in conductivity of the lipid phase, unmatched by any other substance found in nerves. Nerve impulses are negative charges, and onium ions in general, and acetylcholine in particular, possess the ability to create such charges. Their physiological effects parallel the dipole moments and dissociation constants of the corresponding acids, and are affected by molecular changes (ethyl instead of methyl groups on the quaternary nitrogen) which determine their phase–boundary potential, that is, their pharmacodynamic action.[58] This interesting observation underscores the current state of flux of these ideas, and the many factors which will have to be considered before a really satisfactory theory is evolved.

VI. AN AUTONOMIC INTERPRETATION OF ANALGETIC ACTION[54]

The theories correlating analgesia with central nervous depression have met with the difficulty of explaining why the peaks of the two effects are not encountered simultaneously. Moreover, the excitation produced by morphine in the cat and in man is hard to reconcile with explanations of depression. If analgetic action were solely a manifestation of central depression, analeptic drugs such as amphetamine should counteract the effect of morphine; but this effect is actually enhanced by amphetamine. It is also increased by ephedrine, epinephrine, and by the cholinergic drug, Prostigmin. Vice versa, it is lowered by the cholinergic depressants, scopolamine and atropine. These recent observations have served as a basis for an adrenergic theory of analgesia, and perhaps a cholinergic theory of pain. However, certain cholinergic agents (Doryl) can add to the analgetic effect produced by injected epinephrine. The pharmacodynamic mechanism of this action is as yet uncertain; it may be that the parasympathomimetic drug stimulates the output of epinephrine by the adrenal gland which can then enhance the peripheral adrenergic vasoconstrictor

[57] Barnes and Beutner, *Nature*, **164,** 109 (1949); *Science*, **110,** 511 (1949).
[58] Holmes, Jenden, and Taylor, *Nature*, **159,** 86 (1947).

TABE III. ATOMIC DISTANCES IN ANALGETIC DRUGS.

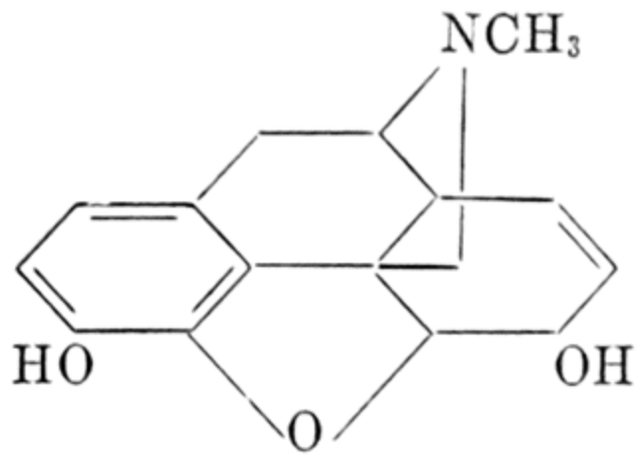
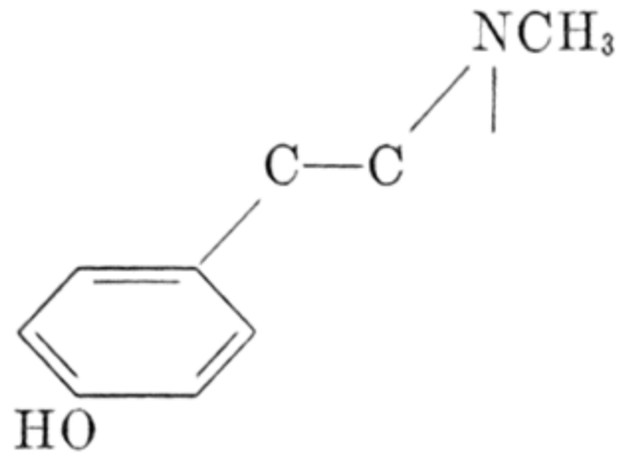
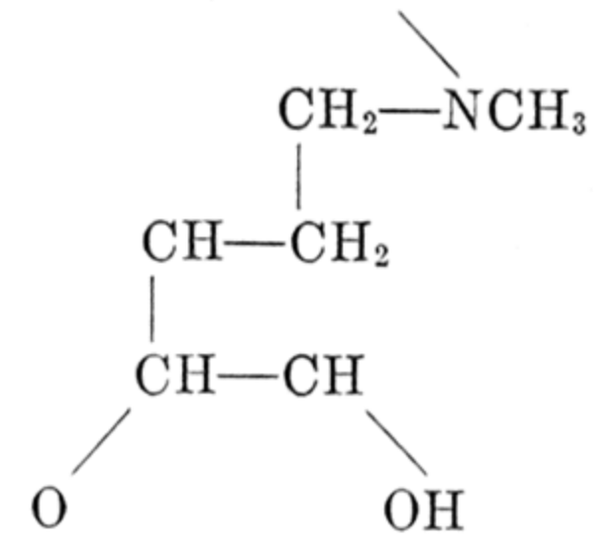
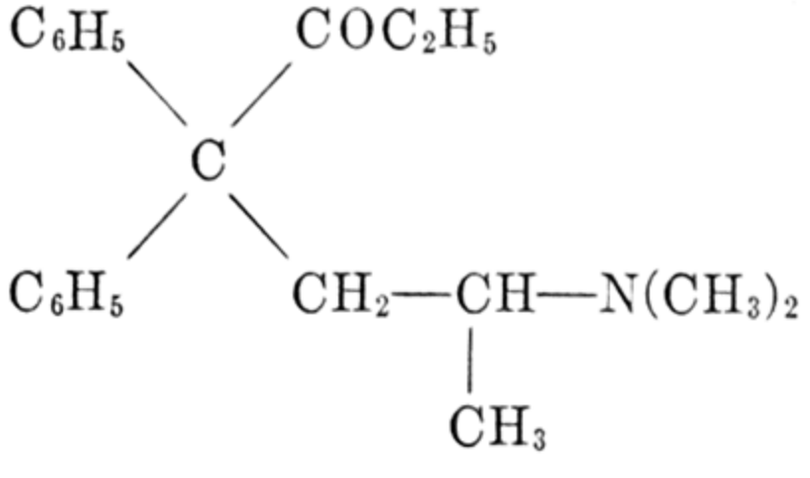
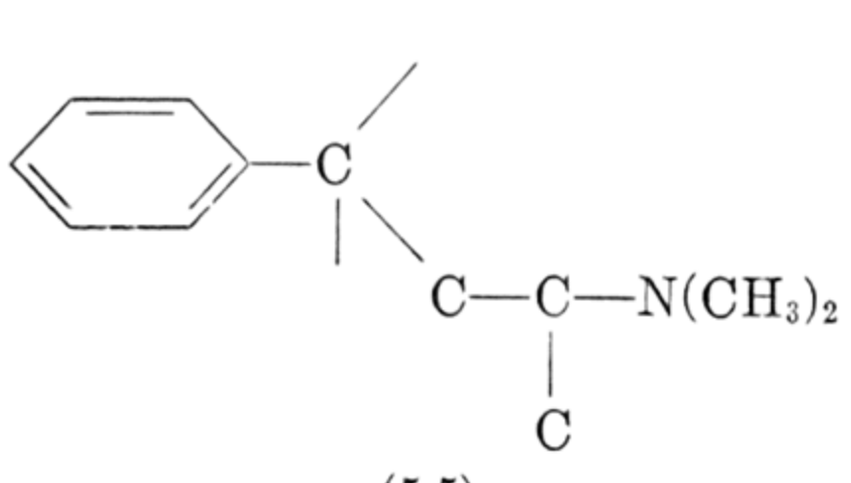
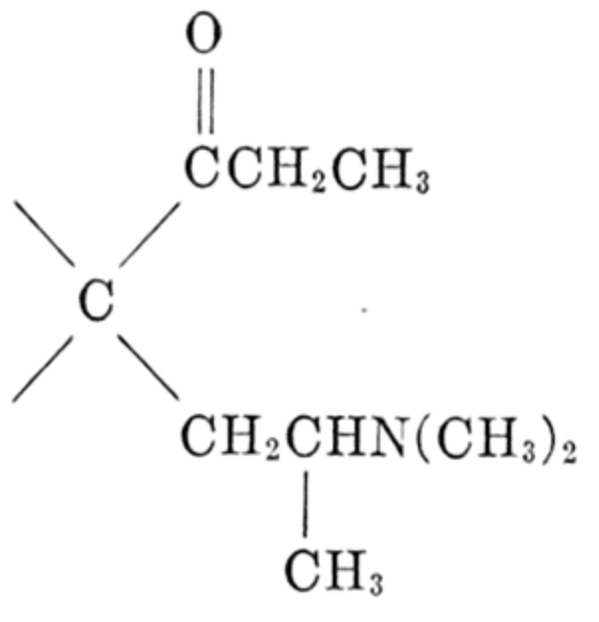
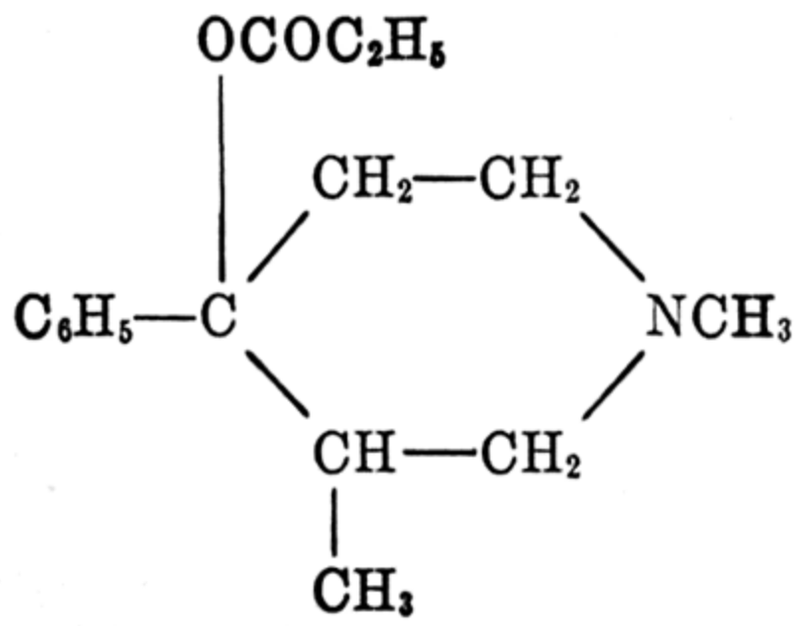
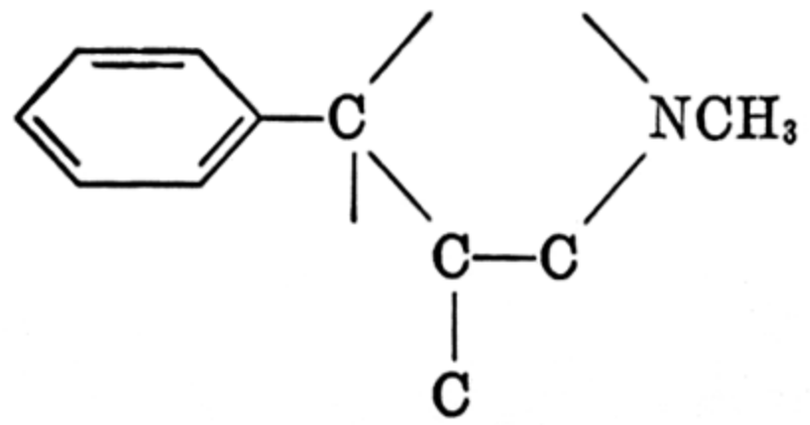
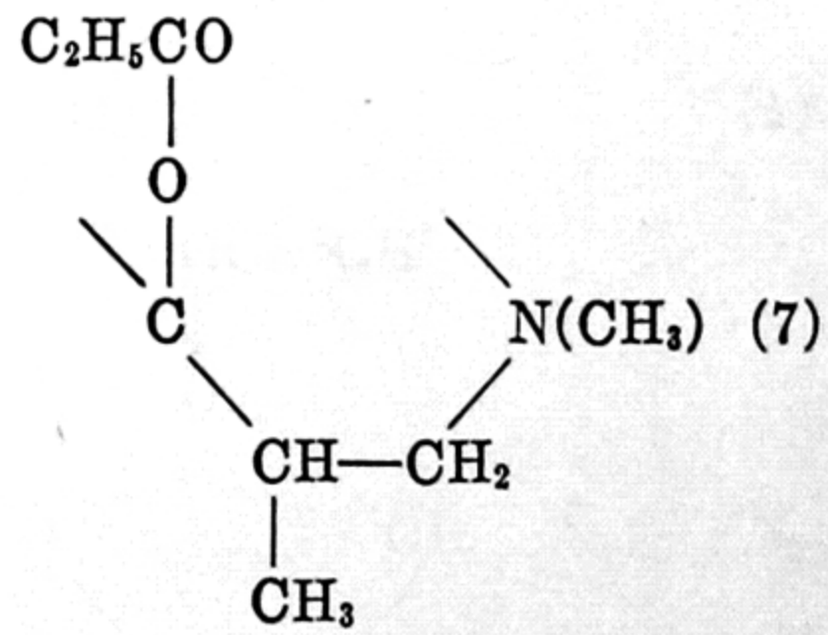
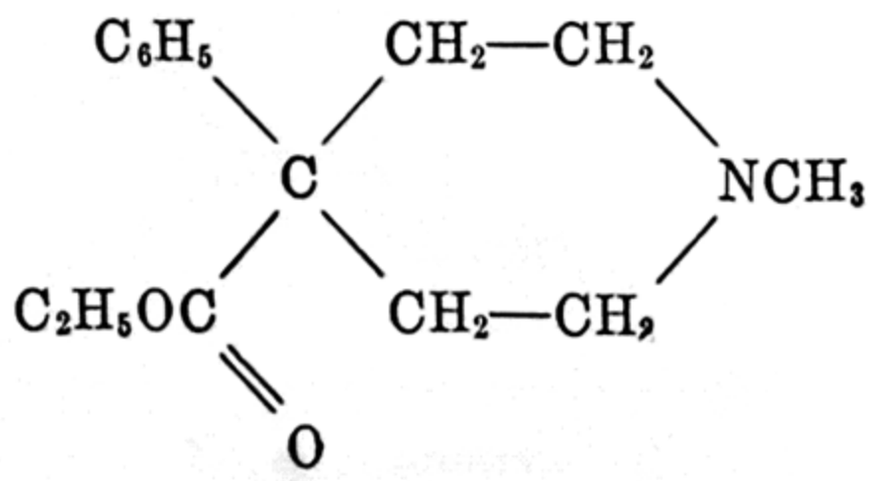
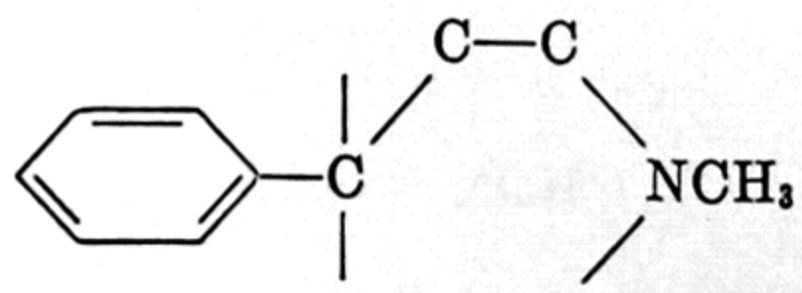
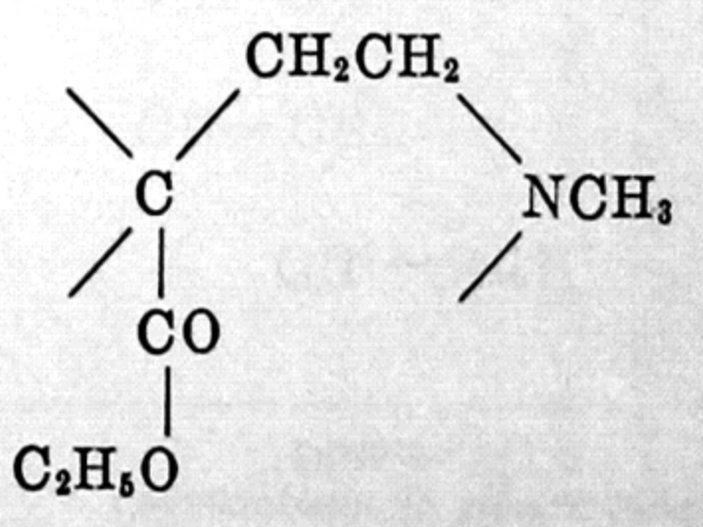
Drug Name	Structure	Sympathetic Moiety (and Distance, Å)	Parasympathetic Moiety (and Distance, Å)
Morphine		 (5)	 (6)
Methadon		 (5.5)	 (7)

Table continued

TABLE III. ATOMIC DISTANCES IN ANALGETIC DRUGS (*Continued.*)

Drug Name	Structure	Sympathetic Moiety (and Distance, Å)	Parasympathetic Moiety (and Distance, Å)
1,3-Dimethyl-4-phenylpiperidinol-4-propionate		 (5.5)	 (7)
Demerol		 (5.5)	 (7.5)

effect, and this is one of the causes of analgesia.[59] Based on this observation, a theory correlating interatomic distances of analgetics, and analgetic activity conceived as an autonomic function has been proposed.

It is possible to scan in the molecules of morphine and morphine-like analgetics, atomic groupings which could be interpreted as sympathomimetic and parasympathomimetic moieties, respectively. These groups are listed in Table III for a few representative analgetics together with two distances for each compound as calculated from atomic scale models; (*a*) the sympathetic distance, the average maximum distance between the first carbon of any alkyl group of the amino nitrogen atom, and the aromatic carbon atom to which the alkylamine chain is attached; (*b*) the parasympathetic distance, the average maximum distance between the first carbon of any alkyl group on the amino nitrogen, and the terminal oxygen atom.

[59] Buscaino and Pero, *Riv. patol. nervosa e mentale*, **58,** 153 (1941); *Chem. Abstr.*, **42,** 3490a (1948). Pero, *Giorn. ital. anestesia e analgesia*, **5,** 128 (1939); *Chem. Abstr.* **42,** 3489i (1948).

CHAPTER XXII

Curare and Curariform Drugs

I. CURARE

The South American arrow poison curare[1] produces paralysis of voluntary muscles characterized by dropping of the eyelids, drowsiness, paralysis of the muscles controlling the neck, vocal cords, the extremities, and the diaphragm. Death from curare poisoning is due to respiratory failure and not to other toxic effects as shown by the fact that animals given artificial respiration will tolerate many times the lethal dose of the drug.

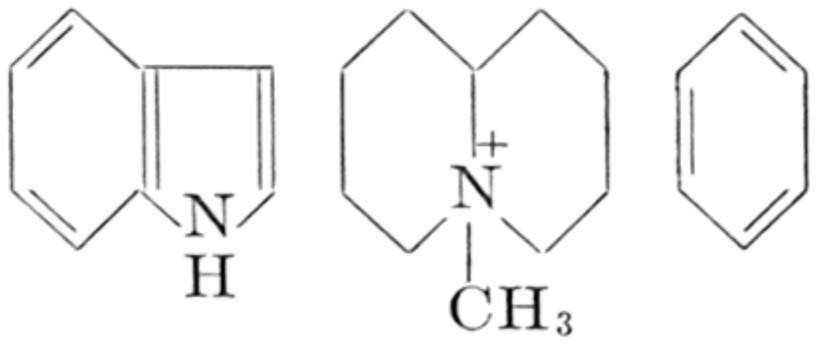
Therapeutic doses of curare have been used clinically to relax muscles in neuromuscular disorders involving spastic, convulsive and paralytic conditions, and in surgery. One of the main uses of curare is in preventing bone fractures during shock therapy in mental patients. These applications are based on the action of curare at the junction of nerve and voluntary muscle, the myoneural junction. As explained in Chapter XIX, the somatic nerves liberate acetylcholine at this junction, and this hormone stimulates the muscle. The enzyme cholinesterase hydrolyzes acetylcholine rapidly and each new nervous impulse builds up again the critical concentration of acetylcholine to which the muscle responds.[2] Too little acetylcholine does not stimulate the muscle, while too much (as in parenteral injection of acetylcholine or certain inhibitors of cholinesterase) leads to curare-like paralysis. Curare does not inhibit cholinesterase nor does it prevent the liberation of acetylcholine. It appears to cause peripheral paralysis by raising the threshold of excitation of the muscle so that no response is elicited by normal amounts of acetylcholine.

The result of curarization is to render the muscle "sole" under the nerve end-plate inaccessible to the normal transmitter, acetylcholine. The stability of the curare alkaloids permits their occupation of this sole for considerable periods, thus blocking access of acetylcholine which is itself a quaternary base of very high wave potential.

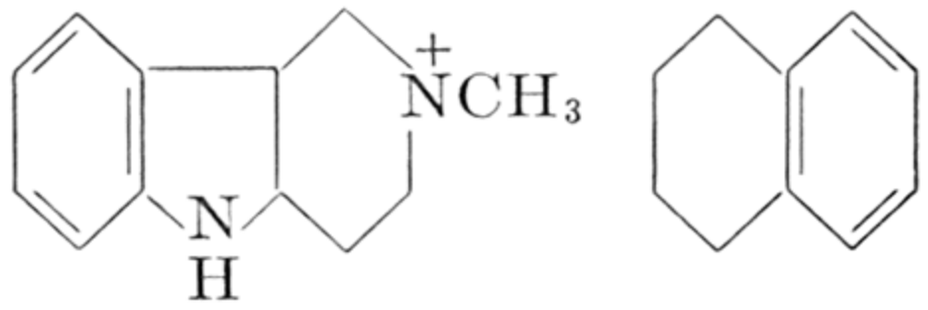
[1] Craig, *Chem. Revs.*, **42,** 285 (1948).
[2] Rosenblueth and Morison, *Am. J. Physiol.*, **119,** 236 (1937). Taylor, *Ann. chim. anal. chim. appl.*, **19,** 33 (1937).

Curare-like, or curariform, activity is not easily reproduced quantitatively with different batches of curare. This uncertainty stems from the poorly controlled specimens of the crude drug which are obtained from the tropics. Depending upon the containers in which they are packed, three types of curare are usually procured. Gourd or calabash curare is the most effective kind; its amorphous alkaloids are not yet fully understood chemically. Tube curare, packed in bamboo tubes, contains *d*-tubocurarine chloride as its active ingredient besides tertiary inactive bases. Pot curare, which is shipped in earthenware pots, has as its active principle some quaternary bases which are probably related to tubocurarine.[3] The botanical origin of the crude drugs is still somewhat obscure but *Chondodendron tomentosum* Ruiz and Pavon,[4] a vine one-hundred feet tall, and several *Strychnos* species and menispermaceous plants have been shown to contain curare.

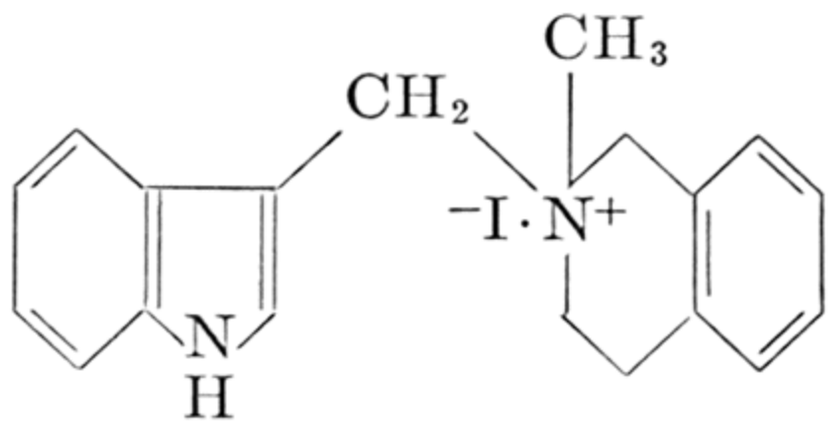
Eighteen alkaloids have so far been isolated from calabash curare, the most active being C-toxiferine-I which paralyzes frogs in doses of 5 to 9 γ/kg. Karrer and Schmid[5] have made probable a β-carboline structure, or perhaps a γ-carboline structure containing one secondary and one quaternary nitrogen atom for some of the calabash curare alkaloids. In order to test similar compounds, N-(3-indolylmethyl)-N-methyl-1,2,3,4-



Parts of β-Carboline Structure



Parts of γ-Carboline Structure



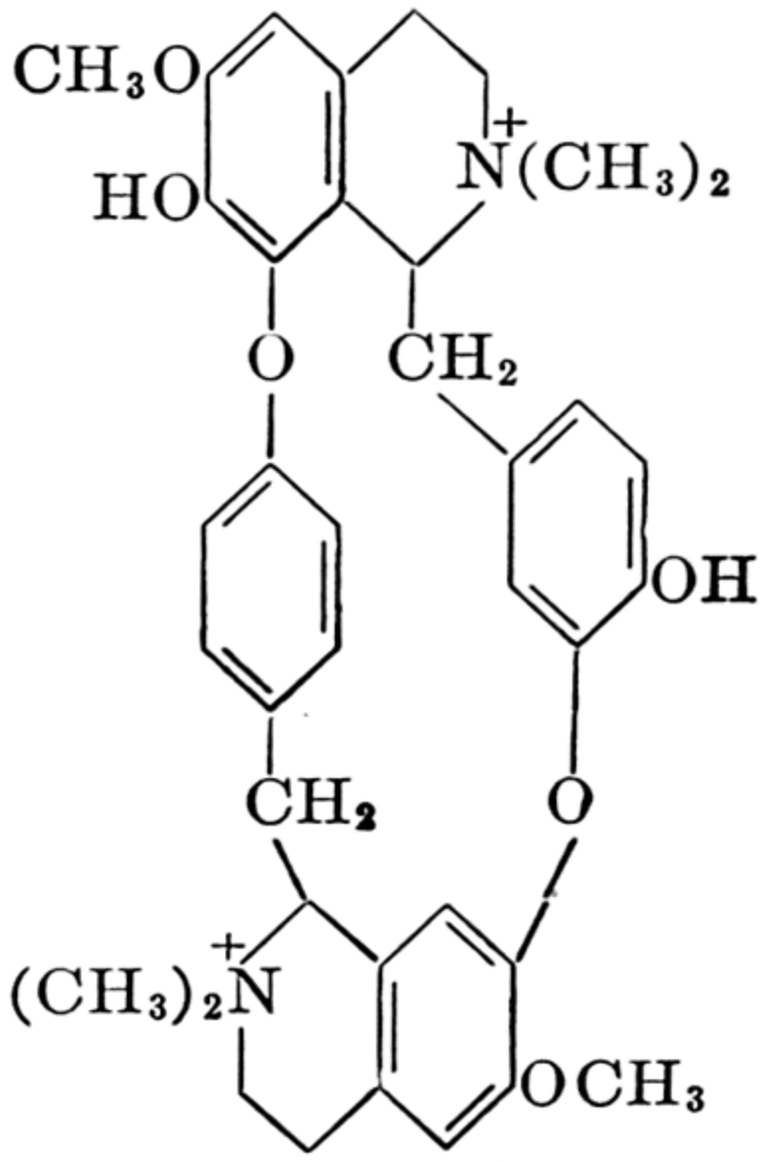
(XXII-1)

tetrahydroisoquinolinium iodide (XXII-1), an open-chain analog of the

[3] King, *J. Chem. Soc.*, 1381 (1935); 1276 (1936); 1472 (1937); 1157 (1939); 737 (1940).
[4] Wintersteiner and Dutcher, *Science*, **97,** 467 (1943).
[5] Karrer and Schmid, *Helv. Chim. Acta*, **29,** 1853 (1946). Schmid and Karrer, *ibid.*, **30,** 1162 (1947). Schmid, Ebnöther, and Karrer, *ibid.*, **33,** 1486 (1950). Wieland, Witkop, and Bähr, *Ann.*, **558,** 144 (1947).

γ-carbolines was prepared by Craig and Tarbell[6] but its activity was not very high. It paralyzed mice in doses of 16 mg./kg.

d-Tubocurarine, now a well-defined standard for the physiological evaluation of curariform activity, is a phenolic bis-benzylisoquinolinium alkaloid the structure of which (XXII-2) has been established through the degradative experiments of Späth,[7] and of King.[8]



(XXII-2)

Other active alkaloids from calabash curare include several bases of similar structure which contain only one quaternary cyclic nitrogen. Some of them, for instance *d*-chondocurine, have no quaternary nitrogen at all, but their activity is correspondingly low; the dimethochloride of *d*-chondocurine, however, has about three times as prolonged and powerful a paralyzing action as *d*-tubocurarine.

Methylation of the free phenolic hydroxyl groups of *d*-tubocurarine leads to more active curariform compounds, but ethylation and butylation produce less active, or inactive derivatives. Nitration or bromination of one of the alkaloids from calabash curare, calabashcurarine I, gives drugs which paralyze frogs at the low dose of 8 γ/kg.

Like the crude mixtures from which it is derived, *d*-tubocurarine is ineffective orally and has a low therapeutic index. This holds also for

[6] Craig and Tarbell, *J. Am. Chem. Soc.*, **71,** 462 (1949). Boekelheide and Ainsworth, *ibid.*, **72,** 2132, 2134 (1950).
[7] Späth and Kuffner, *Ber.*, **67,** 55 (1934).
[8] King, *J. Chem. Soc.*, 265 (1948).

Intocostrin, a standardized, purified curare preparation which is used clinically instead of the less easily purifiable homogeneous alkaloids. Therefore, many other compounds have been tested for curariform activity with the hope of finding an orally active drug having a wider margin of safety.

The most usual procedure for measuring curariform paralysis is the rabbit head drop method in which the compound is injected intravenously into the ear of a rabbit until the animal can no longer lift its head in three minutes. It is important that a good curariform drug exert no stimulating nicotinic action, the stimulatory component of the action of acetylcholine. Any muscarinic activity could well be counteracted by simultaneous administration of atropine without detracting too much from the paralyzing ability of the drug.[9]

II. ERYTHRINA ALKALOIDS

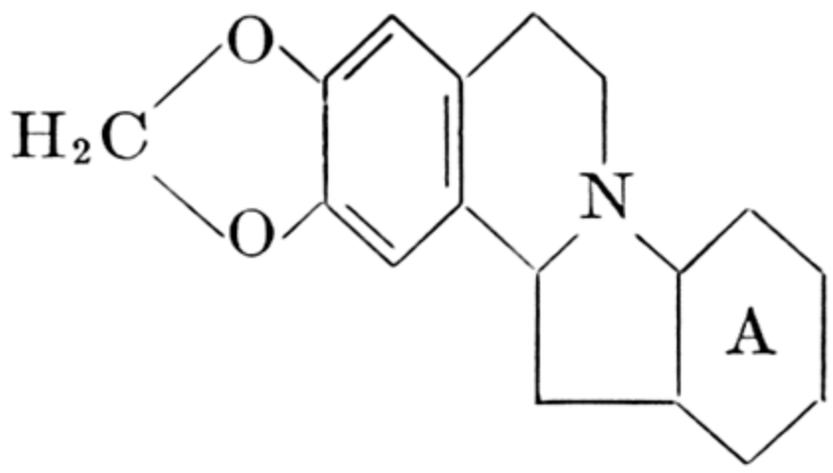
Since the most active curare alkaloids are quaternary ammonium salts, and the less powerful ones acquire more prolonged activity on quaternization, it became profitable to look for curariform action among other quaternary onium salts. As will be seen below, curariform activity and presence of a quaternary ion have virtually become synonymous. It was therefore surprising to find pronounced curare activity in a series of alkaloids which lack this structural feature. These alkaloids, isolated from the seeds of plants of the *Erythrina* species, have been studied extensively by Folkers and his coworkers since 1939. The most readily obtainable erythrina alkaloid, β-erythroidine, contains a tertiary nitrogen atom common to two rings, two olefinic double bonds, a lactone, and a methoxyl group. Its structure is still uncertain. Neither β-erythroidine nor its dihydro derivative are as powerful as the most active curare alkaloids but they are effective orally and less toxic than the latter in therapeutic doses.

When β-erythroidine is heated with sulfuric acid at 120°, it is demethylated to *apo*-β-erythroidine which exhibits muscle-relaxant properties similar to those of Myanesin (see below).

Another group of erythrina bases which has not been used clinically comprises the compounds erythramine (XXII-3), erythraline (XXII-4) and erythratine (XXII-5) as well as certain others which seem to be acetosulfonates of phenolic parent compounds. The former are tetracyclic compounds containing a methylenedioxy ether group, and a tertiary nitrogen atom common to three rings. The bases differ by their content of hydroxyl

[9] Hunt, *J. Pharmacol. Exptl. Therap.*, **28,** 267 (1926). Hunt and Renshaw, *ibid.*, **25,** 315 (1925).

and methoxyl groups as well as the degree of unsaturation in the terminal six-membered carbon ring (A).



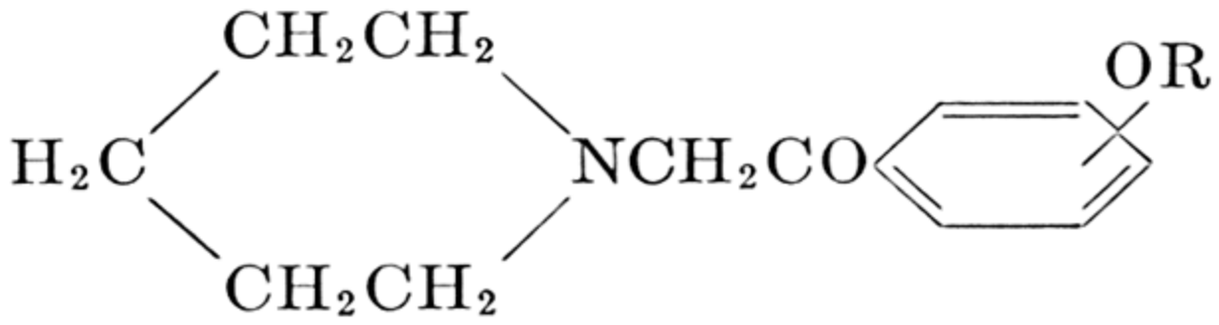
XXII-3: CH_3O, one double bond

XXII-4: CH_3O, two double bonds

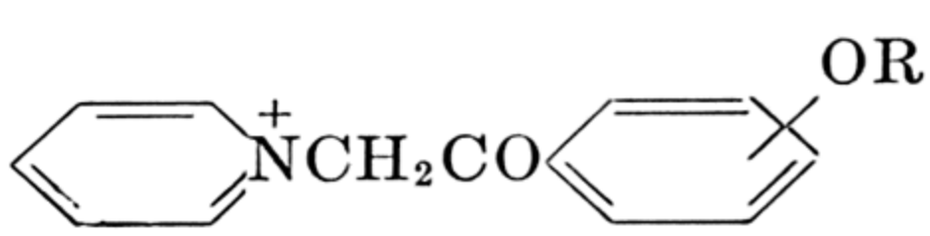
XXII-5: CH_3O, OH one double bond

In contrast to all other known bases, none of the erythrina alkaloids show an increase of curariform action when they are converted to the methiodides. In fact, their activity is decreased 95% by this procedure. Since the structure of erythroidine has not yet been established, it is to early to draw a valid conclusion from this apparent incongruity.

The curarizing effect of N-alkoxyphenacylpiperidines (XXII-6) may be mentioned in this connection.[10] The action of these tertiary amino



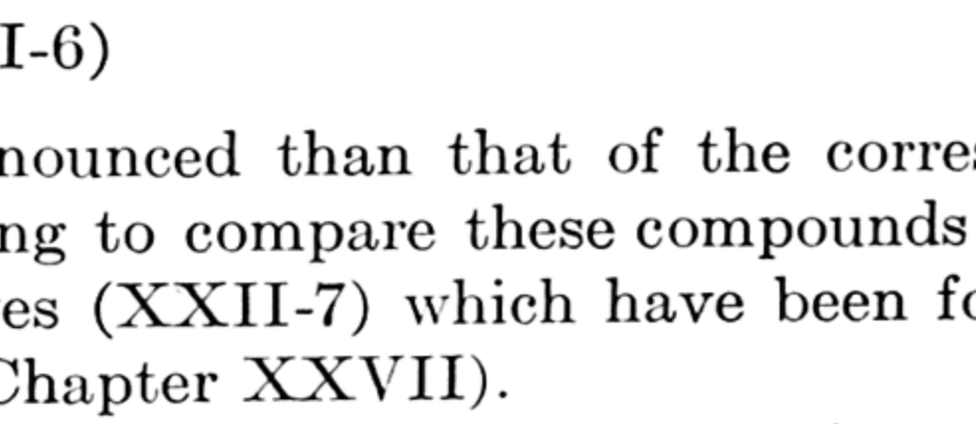
(XXII-6)



(XXII-7)

ketones is more pronounced than that of the corresponding quaternary salts. It is interesting to compare these compounds with alkoxyphenacyl pyridinium derivatives (XXII-7) which have been found to have tumor-necrotizing ability (Chapter XXVII).

The observation that β-erythroidine potentiates the effect of *d*-tubocurarine[11] points to the possibility of drug combinations in the curariform series. Not only alkaloids, but other drugs as well may enter into potentiating combinations. Thus, carbaminoylcholine in very small doses greatly enhances and prolongs the curarizing effect of β-erythroidine.[12]



(XXII-8)

[10] Wilkinson and Copp, British Pat. 617,709 (1949).
[11] Berger and Schwartz, *J. Pharmacol. Exptl. Therap.*, **93,** 362 (1948).
[12] Unna, Kniazuk, and Greslin, *ibid.*, **80,** 39 (1949).

The alkaloid coclaurine (XXII-8), although a secondary cyclic amine, has weak curare properties. This compound emphasizes the variety of structures capable of producing peripheral paralysis.[13] N-Methyl-emetine-N,N′-diethosulfate has also been shown to be one-fourth as active as tubocurarine in rabbits.[13a]

III. CURARIFORM ACTION OF ONIUM SALTS

The quaternary nature of the curare alkaloids led Brown and Fraser[14] to the conclusion that the peculiar action of these drugs was due to their onium structure. Later, Hunt and Renshaw[15] investigated a large number of quaternary salts and corroborated the correctness of this prediction. They found that curariform activity increases in intensity from tetramethyl stibonium to tetramethylammonium salts as follows: $(CH_3)_4Sb^+ < (CH_3)_4{}^+As < (CH_3)_4P^+ < (CH_3)_3S^+ < (CH_3)_4N^+$. The tetraethylammonium ion has the least curariform effectiveness while tetramethyl- and trimethyl-alkyl-ammonium salts are most active. Trimethylbutylammonium salts are almost equivalent to curare in pharmacodynamic tests.

Whatever the exact nature of the reaction of quaternary ammonium salts with cell constituents is, it must be similar or even identical for the many ammonium salts known to produce similar effects. The best explanation of this reaction is an ion exchange with potassium ions whose release at the parasympathetic synapse has been demonstrated experimentally. The release of potassium ions is intimately connected with that of acetylcholine, and ammonium ions are known to produce similar effects as potassium ions.[16]

Almost all organic ammonium salts exhibit muscarinic and nicotinic actions which interfere with their utilization in medicine. This feature can be overcome in some instances. Triethylbenzylammonium $[(C_2H_5)_3NCH_2C_6H_5]^+$ and triethyl phenethylammonium salts $[(C_2H_5)_3NCH_2CH_2C_6H_5]^+$ have pronounced curare, muscarinic and nicotinic activity. The two latter properties can be decreased by branching the carbon atom α to the ammonium nitrogen, e.g., $[(C_2H_5)_3NCH(CH_3)CH_2C_6H_5]^+$. This may be compared with the introduction of an α-methyl group into phenethyla-

[13] King, *J. Chem. Soc.*, 1381 (1935).

[13a] Lasslo and Kimura, *J. Am. Pharm. Assoc.*, **39,** 43 (1950).

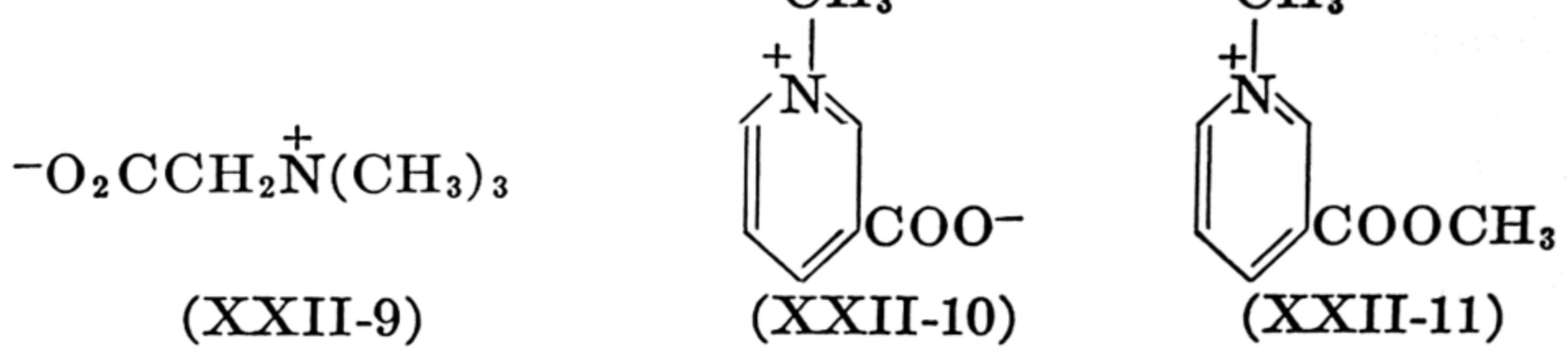
[14] Brown and Fraser, *Trans. Roy. Soc. Edinburgh*, **25,** 151, 693 (1868–1869); *Proc. Roy. Soc.*, **6,** 556 (1869); **7,** 663 (1872).

[15] Hunt and Renshaw, *J. Pharmacol. Exptl. Therap.*, **25,** 315 (1925). Renshaw and Bencowitz, *J. Am. Chem. Soc.*, **47,** 1904 (1925).

[16] Bovet and Bovet-Nitti, *Structure et activité Pharmacodynamique des Médicaments du Système Nerveux Vegetatif.* Interscience, New York, 1948, pp. 701–706.

mine which stabilizes this compound against deamination by monoamine-oxidase.[17]

Of unsaturated ammonium salts, only ethynyltrimethylammonium salts ($CH{\equiv}CN^+(CH_3)_3X^-$) have definite curare action.[18] Aromatic trimethylammonium salts are much less active. When a negative charge is introduced into the same molecule, as in the betaines (XXII-9) and (XXII-10) pharmacological activity is sharply reduced. When the negative



$^-O_2CCH_2\overset{+}{N}(CH_3)_3$ (XXII-9)

(XXII-10)

(XXII-11)

charge is removed by esterification, the resulting ammonium salt (XXII-11) becomes curariform.

A very large number of heterocyclic ammonium compounds, both of the aromatic (pyridinium) and saturated (piperidinium) type have been tested for curare activity. Most of them paralyze voluntary muscles, and this holds also for quaternary methohalides of several alkaloids. None of these compounds have been used since they have too low a margin of safety.

The similarity of tetraalkylammonium salts with the quaternary anchoring group of choline, $HOCH_2CH_2N^+(CH_3)_3\cdot OH^-$, permits the prediction that curare-like properties will be detected among choline derivatives. Even choline itself exhibits weak curariform action, aside from its equally feeble muscarinic and nicotinic components. Simple alkyl ethers of choline ($ROCH_2CH_2N^+(CH_3)_3\cdot OH^-$) are predominantly curare-like, and ethers of thiocholine, for instance, $(CH_3)_2CHCH_2SCH_2CH_2N^+(CH_3)_3\cdot OH^-$, are powerful though brief-acting curariform drugs.

Aryl ethers of choline, especially *m*-bis(β-triethylammoniumethoxy) benzene diiodide (XXII-12), m-$C_6H_4(OCH_2CH_2N^+(C_2H_5)_3I^-)_2$, are strongly curarizing and inhibit true cholinesterase.[19]

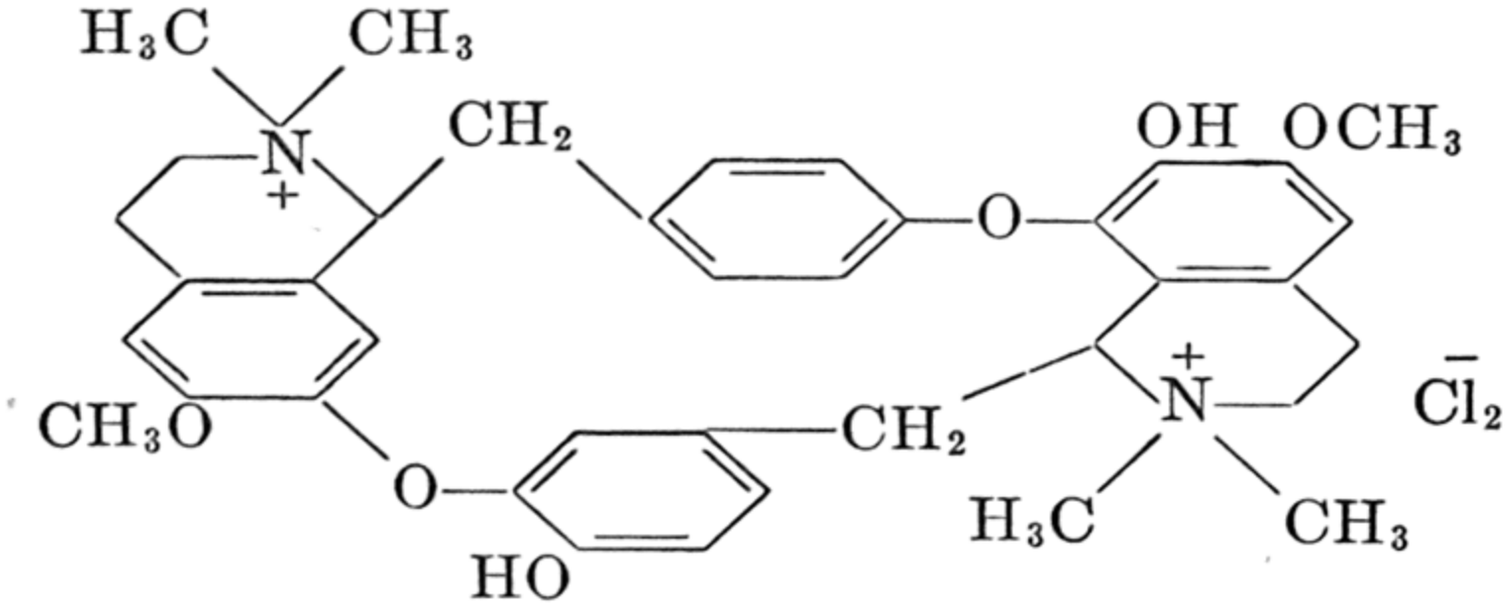
The 1,2,3-tris ether of analogous structure, C_6H_3-1,2,3-$(OCH_2CH_2N^+(C_2H_5)_3I^-)_3$, (Flaxedil) acts like curare but has little paralyzing effect on autonomic ganglia.[20]

[17] Alles, *Univ. Calif. (Berkeley) Pubs. Pharmacol.*, **2,** 161 (1944).
[18] Schmidt, *Ann.*, **267,** 244 (1892).
[19] Bülbring and Depierre, *Brit. J. Pharmacol.*, **4,** 22 (1949).
[20] Mushin, *Lancet*, **1,** 726 (1949).

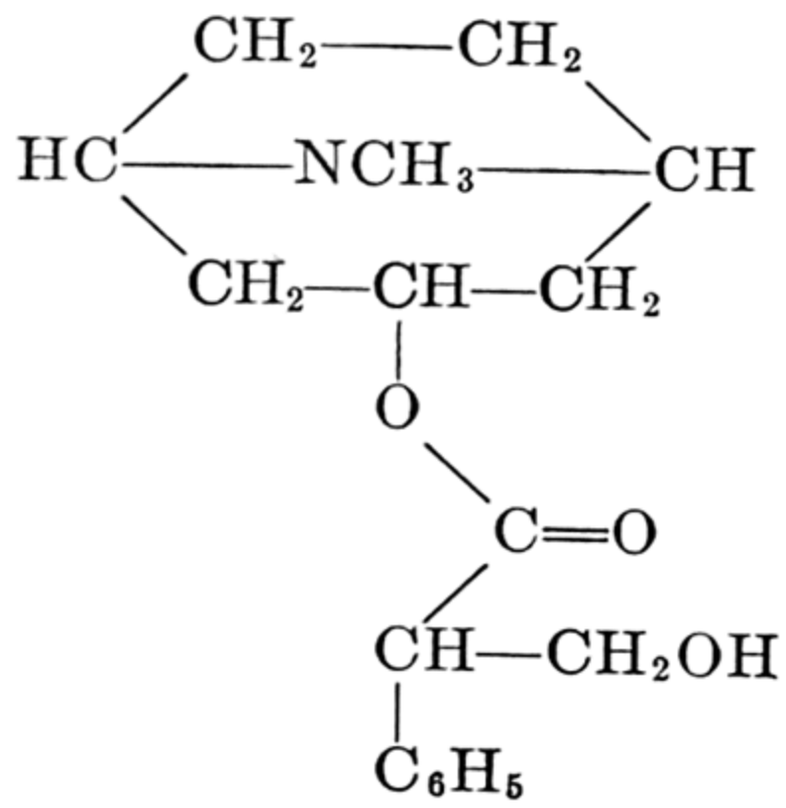
The quaternary carbamate, Prostigmin (XXI-39) paralyzes voluntary muscles only in large doses while its clinical use, the increase in tone of spastic muscles in myasthenia gravis and infantile paralysis, is based on exactly the opposite effect. The mechanism of action of this inhibitor of cholinesterase has been discussed previously.

IV. BIS-ALKYLENE ETHERS, BIS-QUINOLINIUM SALTS AND DIATROPINE DERIVATIVES

As indicated previously, *d*-tubocurarine blocks the nicotinic action of acetylcholine on the skeletal muscles but exerts little effect on autonomic ganglia, involuntary muscles, or glands. The same reasoning of correlating interatomic distances of important molecular points which had been used with muscarinic stimulants and blocking agents can be applied to *d*-tubocurarine. The distance between the N-methyl group and the three oxygen atoms on the same tetrahydroisoquinoline ring of *d*-tubocurarine (XXII-2) is within a radius of 5 to 9 Å, similar to the linear measurements between the analogous groups in acetylcholine. The two groups of ether oxygen atoms of *d*-tubocurarine average 9 Å in their distance from



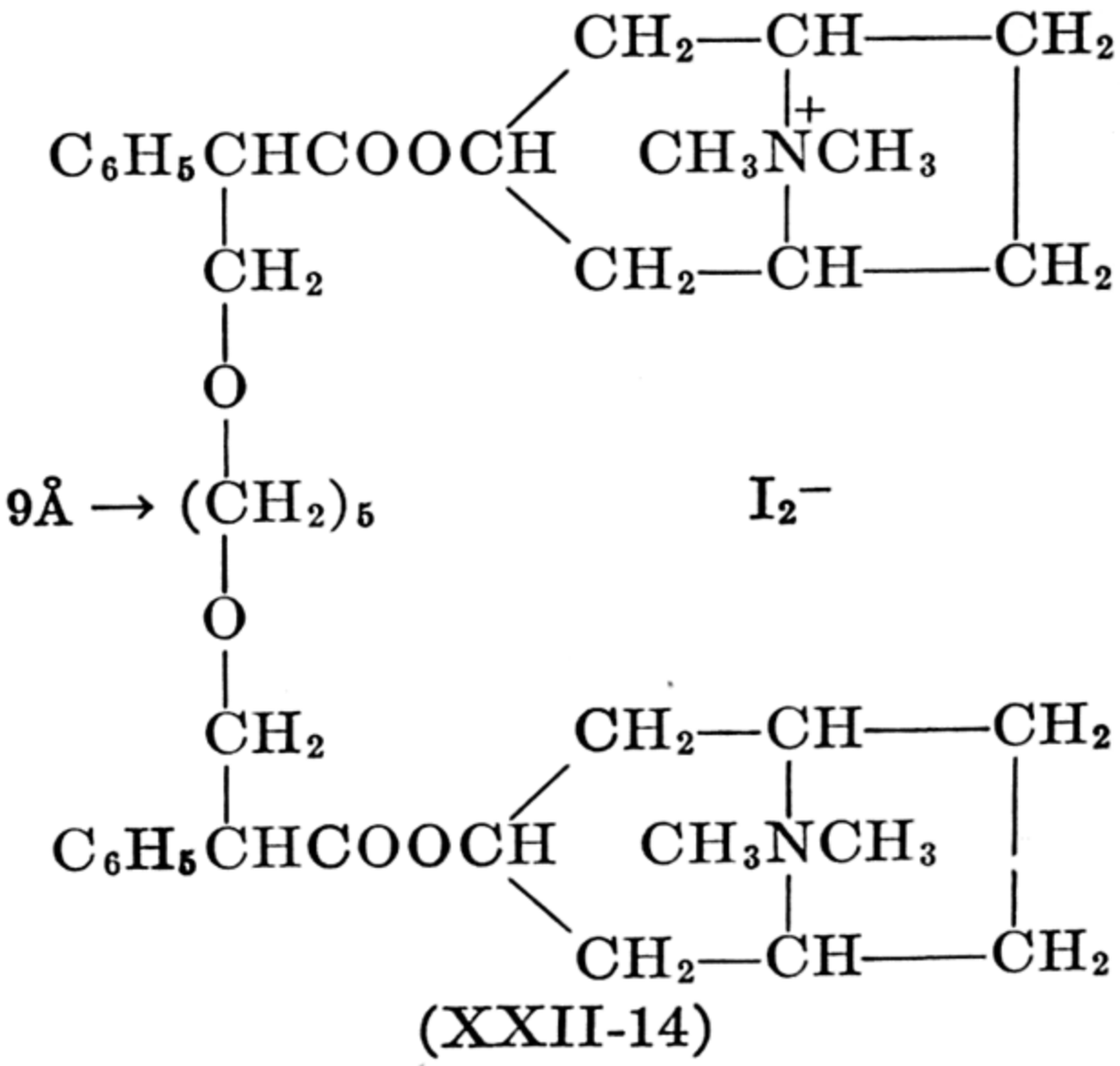
(XXII-2)



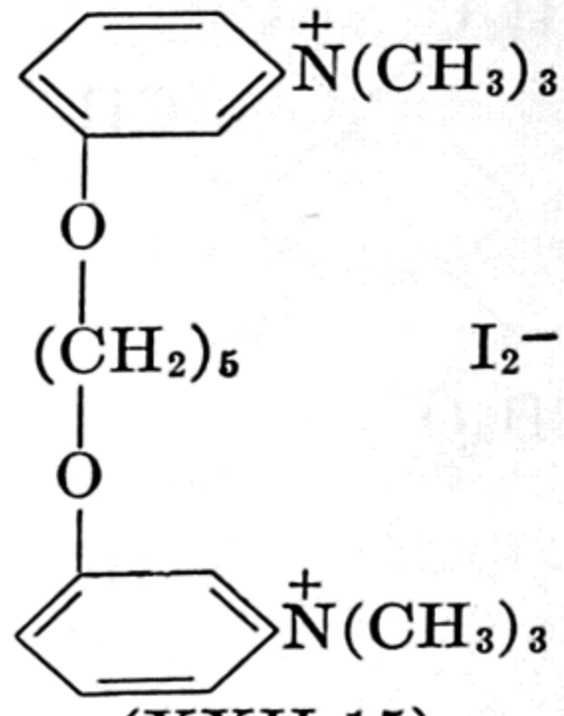
(XXII-13)

each other, and the two quaternary nitrogen atoms are 13 to 15 Å apart.[21] Each "half" of tubocurarine thus resembles the spatial arrangement of atropine which give it an umbrella-like structure. However, it contains twin rows of the oxygen-nitrogen groupings instead of the single row in atropine. It seems, therefore, that the presence of two rows of "prosthetic" groups may be responsible for the specific action of *d*-tubocurarine on the neuromyal junction which is lacking in atropine (XXII-13).

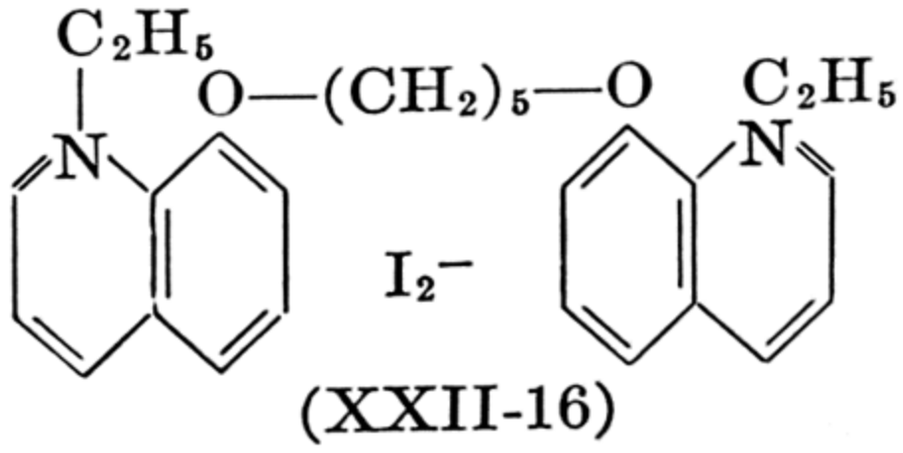
In order to test this hypothesis, two quaternary diatropine derivatives were prepared and found to be highly effective and specific curarizing agents. In joining two methyl atropinium moieties *via* an alkylene ether chain (XXII-14), a five-carbon chain was chosen since Bovet[22] had reported that compounds (XXII-15) and (XXII-16), which also have the two quaternary *o*-aminophenolic groups separated by a distance of 9 Å, are curariform in doses resembling tubocurarine. Compared to atropine methonitrate (Eumydrin), the diatropine derivative (XXII-14) was 10 to 25 times more effective.



(XXII-14)



(XXII-15)

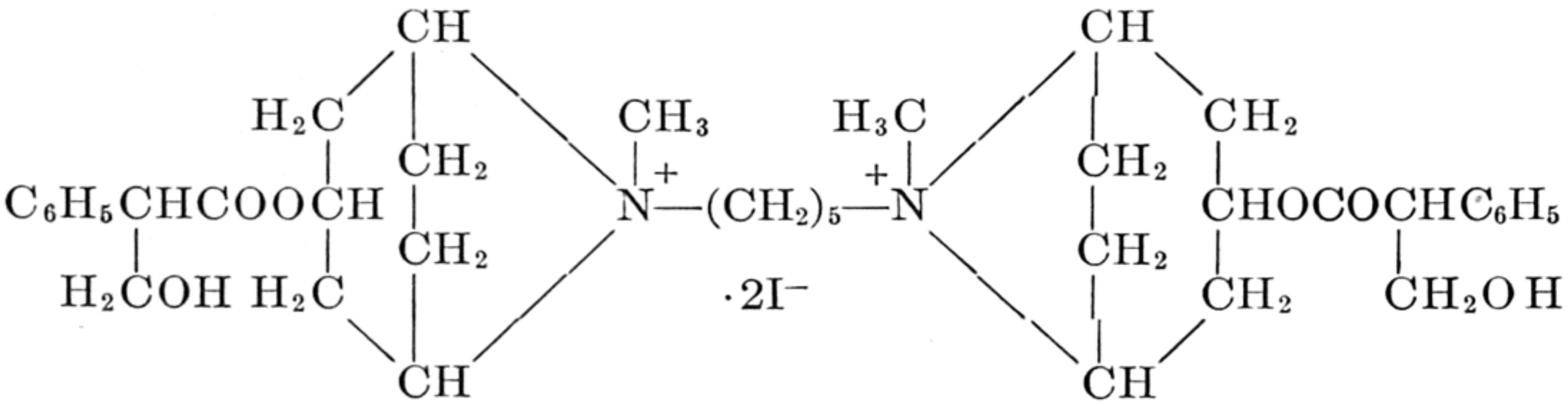


(XXII-16)

[21] Kimura, Unna, and Pfeiffer, *J. Pharmacol. Exptl. Therap.*, **95,** 149 (1949).

[22] Bovet, Courvoisier, Ducrot, and Horclois, *Compt. rend.*, **223,** 597 (1946); **247,** 1733 (1947). Bovet, *Compt. rend. soc. biol.*, **141,** 979 (1947). Grob, Holaday, and McG. Harvey, 41st Meeting, Am. Soc. Clin. Invest., May 1949, p. **24.**

The diatropine derivative (XXII-17) in which the quaternary nitrogens are connected by five carbon atoms is equally strongly curariform although the action of both (XXII-15) and (XXII-16) is less than half that of *d*-tubocurarine. A ten-carbon chain in place of the five methylene



(XXII-17)

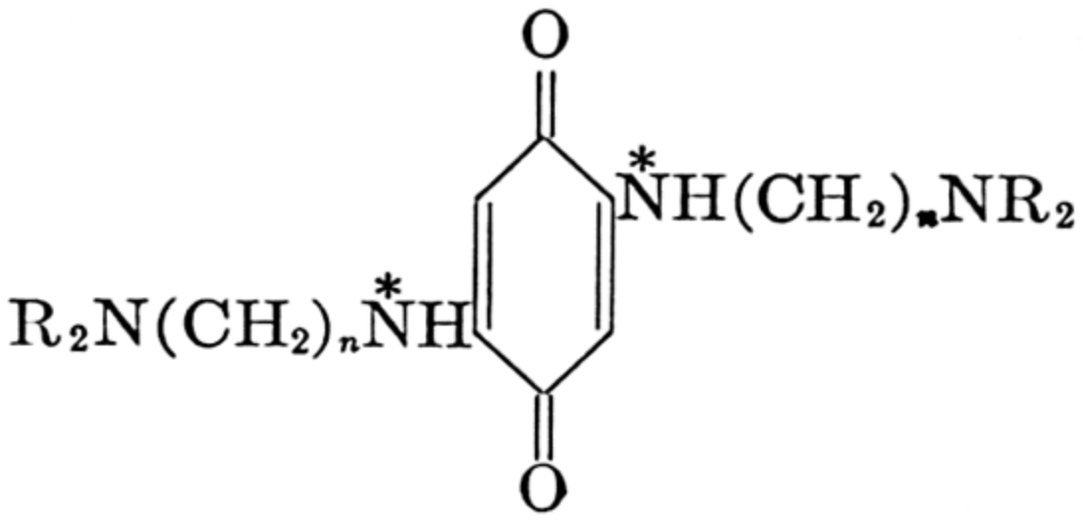
groups in (XXII-17) should give a more efficacious drug since simple aliphatic diquaternary diamines reach maximum curare activity when the distance between the two nitrogen atoms is 15 Å as in tubocurarine.[23] It has been suggested that this principle of diquaternization might be applied successfully to the antihistaminic agent, Benadryl, and other drugs exhibiting moderate atropine activity.

The spacing of long alkylene chains between basic ester groups also leads to curariform derivatives.[24]

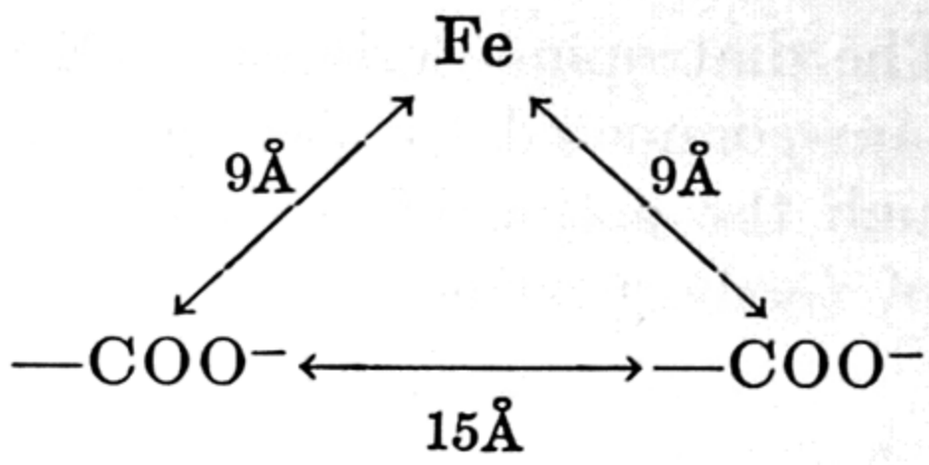
Further support is lent to this hypothesis by the finding of Cavallito[24a] that bis-dialkylaminoalkylamino *p*-benzoquinones (XXII-18) exhibit strong curarimimetic activity. This is compatible with the idea that the two onium heads (*N) are located about 14 Å apart. The other two (aliphatic) tertiary nitrogen atoms do not fit into this scheme; however, since optimum activity is reached when n is 4, the distance $R_2N(CH_2)_4NHQu$ ($\pm$9 Å) must have some relation to two acidic "receptor" groups of a cell substance. This could be a porphyrine-metal complex (XXII-19) which has these two dimensions, and as a further analogy of this possibility the fact may be cited that 2,5-bis-dimethylamino-*p*-benzoquinone (XXII-20) forms copper complexes.

The relation of aliphatic chain length to various pharmacological manifestations of polymethylene bistrimethylammonium salts, $(CH_3)_3N^+(CH_2)_nN^+(CH_3)_3$, has recently been studied.[24b] A sharp maximum for potency in ganglionic block was observed for $n = 5$ to 6; a maximum for

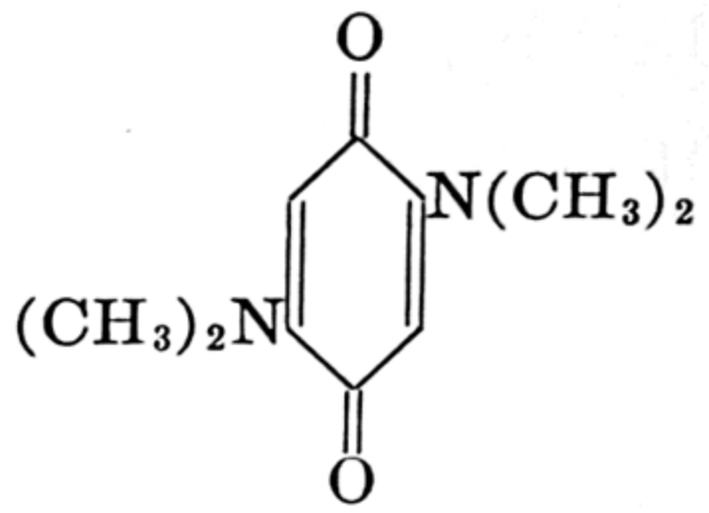
[23] Barlow and Ing, *Nature*, **161,** 718 (1948); *Brit. J. Pharmacol.*, **3,** 298 (1948).
[24] Phillips, *J. Am. Chem. Soc.*, **71,** 3264 (1949).
[24a] Cavallito, Soria and Hoppe, *J. Am. Chem. Soc.*, **72,** 2661 (1950); *Feder. Proc.*, **9,** 287 (1950).
[24b] Paton and Zaimis, *Brit. J. Pharmacol.*, **8,** 381 (1949).



(XXII-18)



(XXII-19)

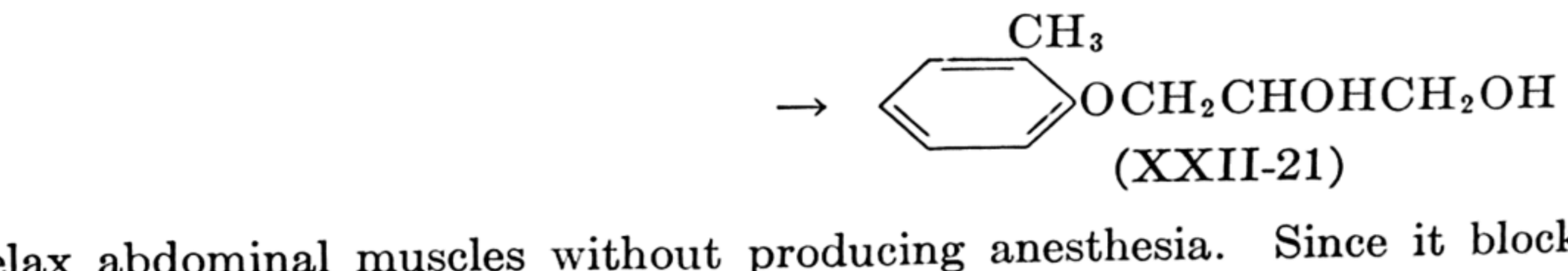


(XXII-20)

potency in neuromuscular block occurred when n was 10. With twelve carbon atoms separating the two quaternary salt groups, a less well defined maximum for muscarine-like activity and anticholinesterase properties was seen. Incidentally, a rise in antibacterial and surface activity began for $n = 12$ and continued beyond $n = 18$ (see Chapter XLIII).

V. GLYCERYL ETHERS AS MUSCLE RELAXANTS

Numerous alpha-glyceryl ethers depress reflexes in the spinal cord in small doses and cause curariform peripheral paralysis in larger dosages.[25] Of the approximately 150 derivatives tested, the relatively non-toxic α-(*o*-tolyl)glyceryl ether (XXII-21) has been introduced into therapy under the names of Myanesin or Tolserol. It is prepared from sodium *o*-cresolate and 1-chloropropane-2,3-diol and owes its medicinal value to its ability to



(XXII-21)

relax abdominal muscles without producing anesthesia. Since it blocks transmission of nervous impulses by acetylcholine at the upper ganglia, it can counteract effectively the tremors of Parkinsonism. These tremors can

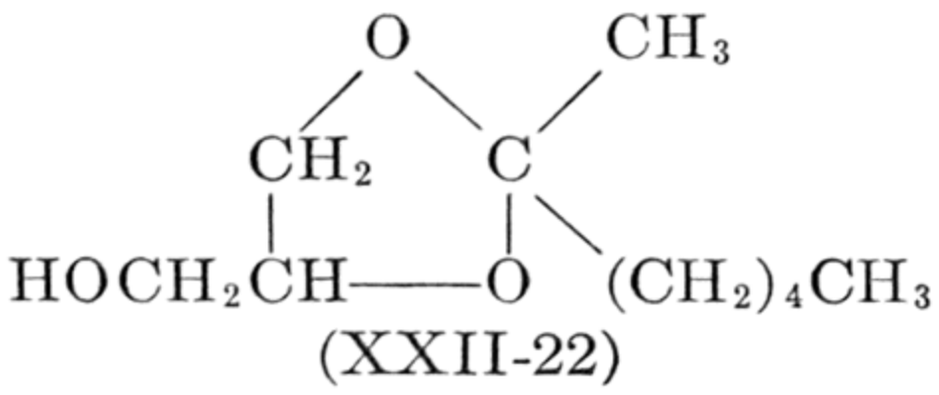
[25] Berger and Bradley, *Brit. J. Pharmacol.*, **1,** 265 (1946). *Lancet*, **252,** 97 (1947).

be treated to some extent with belladonna alkaloids but Myanesin lacks the mydriatic and desiccant side-effects of these drugs.[26]

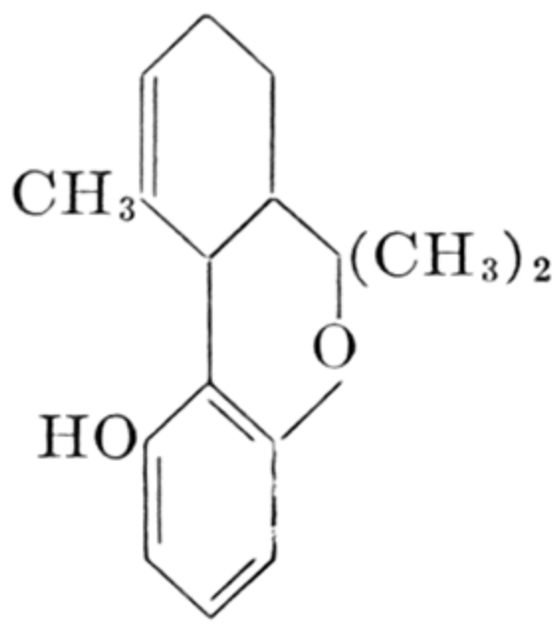
Myanesin is detoxicated rapidly in the body by oxidation of the terminal primary alcohol group to carboxyl. The resulting acid is then excreted.

$$o\text{-}CH_3C_6H_4OCH_2CHOHCH_2OH \rightarrow o\text{-}CH_3C_6H_4OCH_2CHOHCO_2H$$

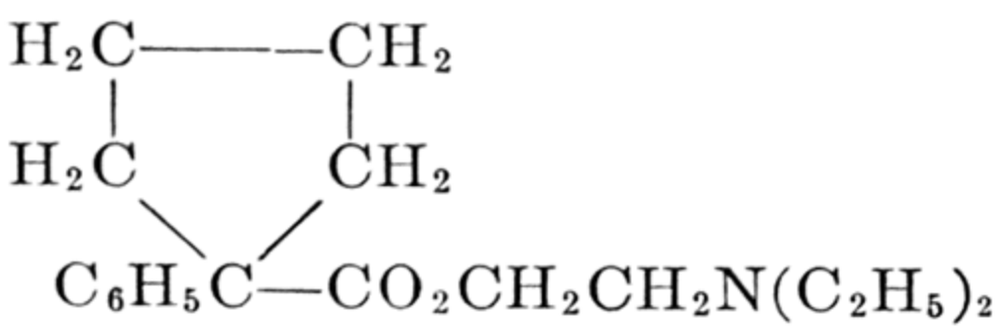
Another drug containing the glycerol grouping is 2-methyl-2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane (Glyketal, XXII-22) which was recently described by Berger.[27] It has been used to relax muscles as an adjunct to surgical anesthesia, to abolish muscle spasm arising from inflammation of the cord in poliomyelitis, or from strychnine poisoning. Glyketal is about one-half more active, but also more toxic than Myanesin. It is interesting to compare its formula with that of cannabadiol (XXII-23) which also produces ataxia at small dosages. Both drugs contain the $—R_2C—O—$ group in cyclic form. The non-cyclic diol, 2,2-diethylpropane-1,3-diol,



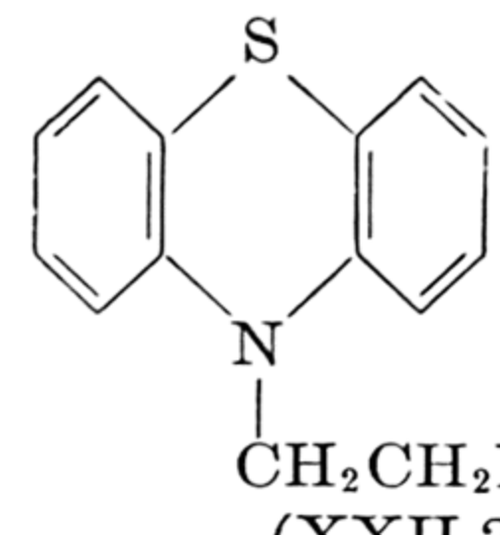
(XXII-22)



(XXII-23)



(XXII-24)



(XXII-25)

[26] Lott, *Trans. N. Y. Acad. Sci.*, **22,** 2 (1948); for further analogs of Tolserol, compare Yale, Pribyl, Braker, Bergeim, Bernstein and Lott, *J. Am. Chem. Soc.*, **72,** 3710, 3716 (1950).

[27] cf. *Ind. Eng. News*, **27,** 3140 (1949). *Federation Proc.*, **8,** 274 (1949).

appears to produce paralysis by affecting higher levels of the central nervous system.[28]

Myanesin-like central effects have been noted in screening certain antispasmodics and antihistaminics. Thus, Panpartit (XXII-24) and Diparcol (XXII-25) have pronounced activity.

In addition to its muscle-relaxing effects, Myanesin has also proved helpful in relieving anxiety, and producing sedation without sleepiness in psychiatric patients. It has been tested in "hangover" and drug withdrawal.[29]

[28] Berger, Russo and Ludwig, *Federation Proc.*, **9,** 258 (1950).
[29] Schlan and Unna, *J. Am. Med. Assoc.*, **140,** 672 (1949).

CHAPTER XXIII

Antispasmodics

I. GENERAL ASPECTS

Antispasmodics are drugs which decrease or abolish spasm, particularly spasm caused by a violent involuntary contraction of muscles. The normal functions of the muscles thus affected, and of the organs controlled by the spastic muscles, are usually disrupted, and pain of often great severity is felt. By relaxing the spastic state, antispasmodics relieve the pain and promote return of normal metabolic conditions.

The therapeutic applications of antispasmodics are principally concerned with abolishing spasms of involuntary structures, that is, muscles innervated by autonomic nerves. For example, visceral and uterine spasms, spasms of the ureter, the bile duct and the gall bladder may be relieved by these drugs. The smooth muscles controlling the motions of these organs are innervated by postganglionic cholinergic nerves. True antispasmodics are capable of preventing or blocking cholinergic nerve stimulation, or the (muscarinic) action of acetylcholine and similar parasympathomimetic drugs on muscles or glands, by a direct action on these effector organs, without interfering with the production and release of acetylcholine.

Depending upon whether they interfere with the parasympathetic mediator, acetylcholine, or act directly upon muscle cells irrespective of innervation, antispasmodics are sometimes spoken of as neurotropic, and as myotropic or musculotropic. Both actions may be classified as cholinergic blocking, keeping in mind that the parasympathetic nervous system is interpreted as exerting effects virtually indistinguishable from those produced by acetylcholine. Isolated muscles, such as a piece of gut or a virgin uterus, become spastic when suspended between registering hinges in dilute solutions of barium chloride, histamine or Pituitrin. This type of spasm simulates musculotropic spasm in the intact animal. Solutions of acetylcholine, on the other hand, reproduce in excised muscles conditions similar to that observed in neurotropic spasm. Both types of spasm can be abolished by suspending the spastic muscle in a solution of a suitable antispasmodic. The activity of the drug is proportional to the concentration required to bring about complete relaxation. The majority of pharmacologists suspend the muscle in the solution of the antispasmodic and meas-

ure its potency by the concentration needed to prevent occurrence of spasm produced by a standard amount of acetylcholine, histamine or barium chloride which is added to the solution.

In connection with relief from histamine-caused spasm, it will be pointed out later (Chapter XXIV) that the mechanism of antihistaminic action is still obscure. An animal may exhibit violent bronchospasm after being treated with histamine and experience sudden and complete relief after subsequent administration of an antihistaminic drug. The latter can also protect the animal from often enormous doses of histamine. But there is no convincing evidence for the assumption that excessive amounts of naturally formed histamine produce clinical asthmatic and related spasms. Because most typical antihistaminic drugs possess some anesthetic properties, their effect on spastic body structures has been attributed to a general depressant action on muscles. This may be true of antispasmodics in general: the relaxation of a pathologically contracted involuntary muscle is obviously equivalent to depressant activity directed against violent over-activity. If antispasmodics are regarded from this broader viewpoint, their pronounced overlapping with analgetics becomes understandable (Chapter XI). On the other hand, evidence is accumulating to explain at least part of analgetic conductance as an operation located in the autonomic system. This may provide a better explanation for this convergence of activities in the same drugs.

Spasms of the voluntary (somatic, skeletal, striate) muscles which receive their motoric impulses from the central nervous system are frequently synonymous with paralysis. Since acetylcholine is the recognized mediator of nerve impulses to skeletal muscles, paralysis of these structures may be due occasionally to a lack of acetylcholine produced at the motor nerve endings, or to a pathological increase in the muscle of cholinesterase which destroys the acetylcholine needed for normal functioning. Administration of acetylcholine, or preferably some less readily hydrolyzable analogs (Mecholyl, Furmethide, Prostigmin etc.) which compete with acetylcholine for cholinesterase, spectacularly relieves at least certain paralytic conditions, especially myasthenia gravis. It has also been postulated that in such paralyses some curare-like factor may be the pathological cause of the conditions. Although these mechanisms still need confirmation, they emphasize the difference of spasms of voluntary and of involuntary muscles, and explain the inactivity of the usual antispasmodics in spasms of skeletal structures. The task of a synopsis of antispasmodics is therefore confined, by custom, to those drugs which abolish spasms of muscles with autonomic innervation.

The clinician who sometimes has to make a rapid diagnosis of a spastic condition and must apply a suitable drug for its relief cannot be expected

to consider the possible pathological mechanisms underlying the observed spasm. He would therefore be benefited by the availability of a drug which would combine neurotropic and musculotropic properties. Much of the research in this field has been directed towards this goal. The ultimate value of an antispasmodic is estimated even in screening tests by the degree of its ability to prevent experimental spasms produced by at least three pharmcodynamically different chemicals.

Two well-known alkaloids have long been accepted as standards of the two main types of antispasmodic activity. The opium alkaloid papaverine relaxes muscles made spastic by direct stimulation with histamine or barium chloride. It has become the standard for musculotropic antispasmodics. The alkaloid atropine is the prototype of neurotropic parasympathetic blocking agents. It prevents spasm of smooth muscles inaugurated by acetylcholine, or by the equivalent excitation of parasympathetic nerves.

A third alkaloid, scopolamine which is found in the shrub Henbane (*Hyoscyamus niger*) and elsewhere is not often used now as a standard drug for comparison of antispasmodics because of its less important peripheral, and more pronounced central activity.

Unless antispasmodic activity is expressed as the concentration needed to overcome the effects of spasm-producing drugs or ions, it is often evaluated by comparison with papaverine and atropine. No useful drug has yet been found which rivals the cholinergic blocking properties of atropine. On the other hand, a number of drugs having several times the activity of papaverine, and at the same time a lower toxicity than this opium alkaloid have come into use.

II. PAPAVERINE

1. Manufacture

The isolation of papaverine from opium by G. Merck, its purification, the proof of its structure by Goldschmiedt, and the early syntheses by Pictet, by Späth and Burger, by Kindler and Peschke and others have been reviewed in monographs on alkaloids.[1] The compound is 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (XXIII-1). Because the alkaloid constitutes only 0.8% of opium, the natural supply from this source is inadequate to meet the demand for papaverine as an antispasmodic. Based on syntheses of originally purely scientific significance, several commercial syntheses of papaverine have been perfected. This is one of the few alkaloids which can now be produced by total synthesis from simple

[1] Small and Lutz, "Chemistry of the Opium Alkaloids," Supplement No. 103 to the Public Health Reports, U. S. Govt. Printing Office, Washington, D. C., 1932. Henry, *The Plant Alkaloids*, 4th ed., Blakiston, Philadelphia, 1949.

starting materials. In contrast to ephedrine (Chapter XIX), papaverine contains no asymmetric carbon atom, and the question of stereochemical separation of the synthetic alkaloid does therefore not need to be considered.

Only one process used in the commercial synthesis of papaverine has been divulged (Figure 1).[2] 3,4-Dihydropapaverine (XXIII-6) is manufactured by a modification of the method of Kindler and Peschke from homo-

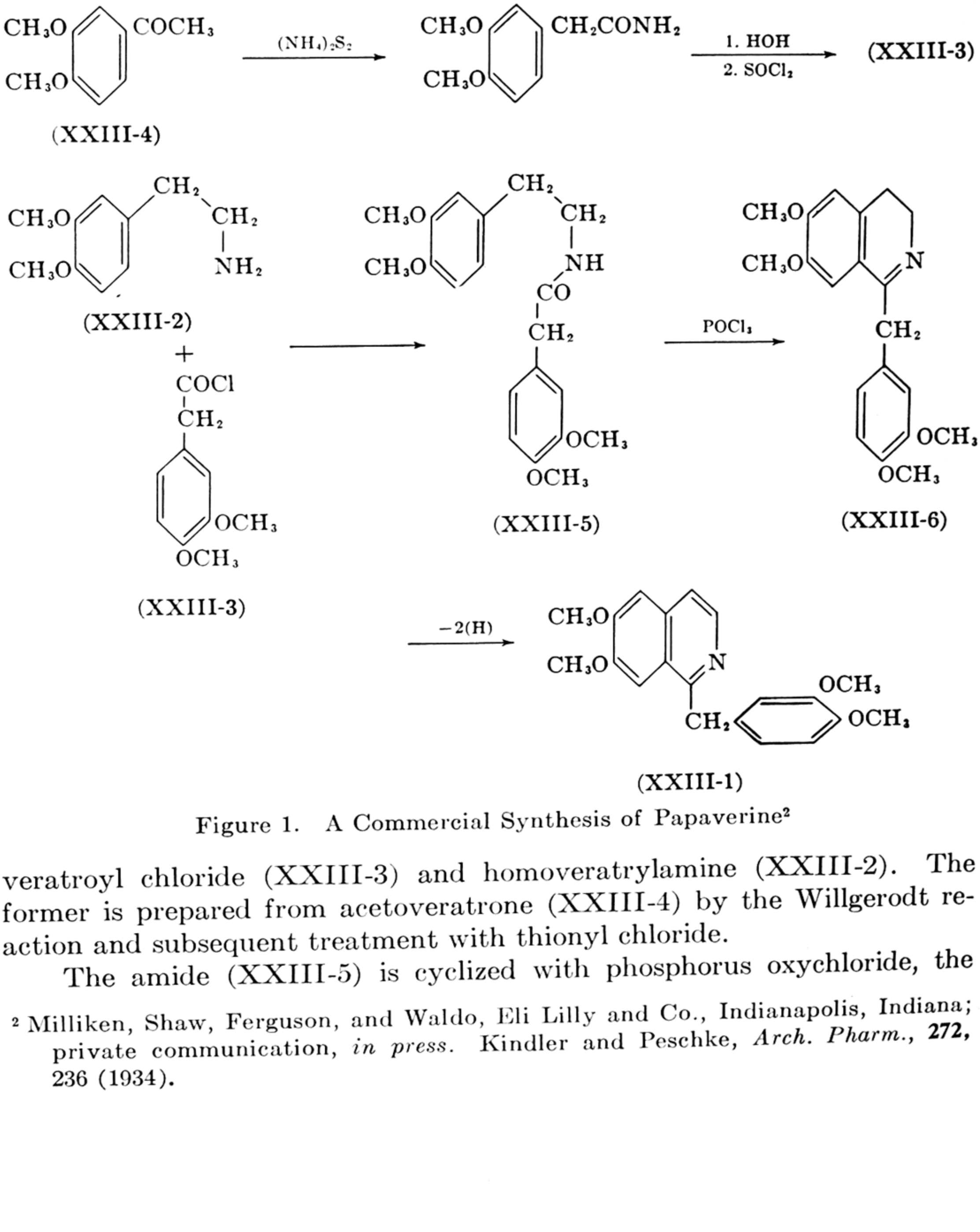


Figure 1. A Commercial Synthesis of Papaverine[2]

veratroyl chloride (XXIII-3) and homoveratrylamine (XXIII-2). The former is prepared from acetoveratrone (XXIII-4) by the Willgerodt reaction and subsequent treatment with thionyl chloride.

The amide (XXIII-5) is cyclized with phosphorus oxychloride, the

[2] Milliken, Shaw, Ferguson, and Waldo, Eli Lilly and Co., Indianapolis, Indiana; private communication, *in press*. Kindler and Peschke, *Arch. Pharm.*, **272,** 236 (1934).

crude 3,4-dihydropapaverine (XXIII-6) washed with caustic and with water, and the dried material is dehydrogenated with palladized charcoal catalyst in decahydronaphthalene solution at 165°.

2. Uses

Papaverine is used clinically as the hydrochloride in doses from 10 to 80 mg. depending on the route of administration. The drug relaxes the smooth muscles of blood vessels, particularly the coronary arteries, as well as those of the bronchi, the viscera, the ureter and the gall bladder. Relaxation is more pronounced if these muscles are spastic. Therapeutic indications for papaverine are arterial embolism and other spastic conditions of the peripheral or pulmonary arteries. Papaverine causes dilation of blood vessels, and has been used successfully to prevent gangrenous conditions, for instance, in ergotism (Chapter XX).

The relaxation by papaverine of smooth muscles other than those of blood vessels is not always as reliable, and atropine and its synthetic congeners are used more widely for such purposes.

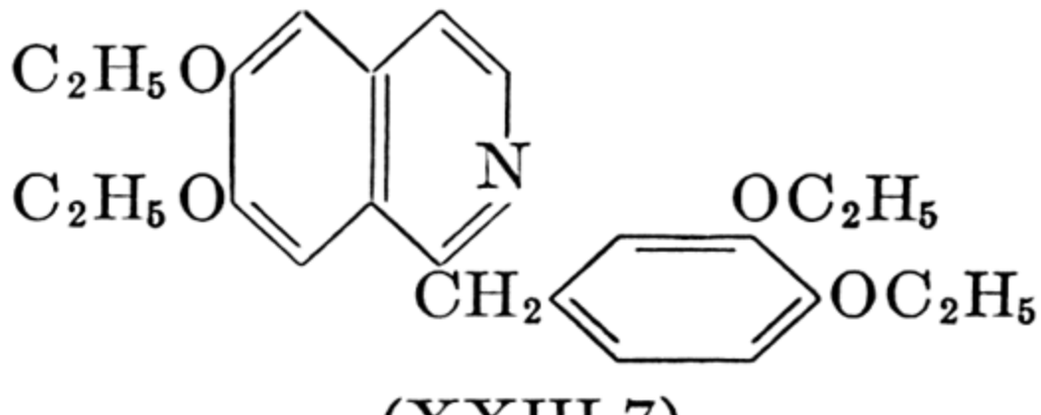
Spastic conditions are produced not only by peripheral nervous disorders, but may be conditioned by superimposition of central nervous impulses. A patient suffering from spastic colitis or angina pectoris will undoubtedly worry about his condition, and by this tax on his central nervous system aggravate his peripheral spasm. Therefore, antispasmodics are frequently administered in conjunction with sedatives or hypnotics. Molecular combinations of papaverine and diethyl barbiturate, papaverine and dipropyl barbiturate, papaverine and phenobarbital (Pavemal), etc. are based on this principle.

III. STRUCTURAL VARIATIONS

1. Variations of Ether and Benzyl Groups

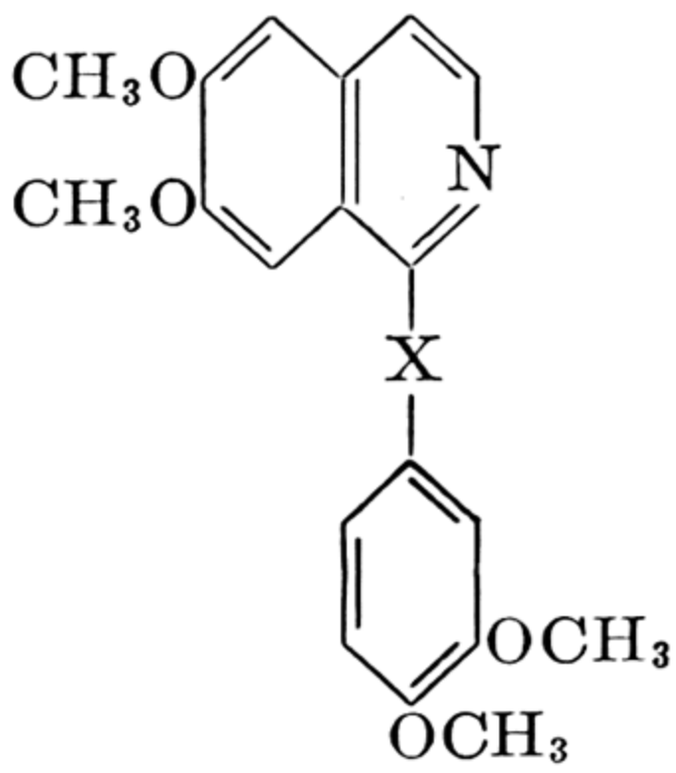
Papaverine and related isoquinoline derivatives are very weakly basic; the salts of the alkaloid react acidic, are easily hydrolyzed and cannot be injected without pain. The alkaline body fluids precipitate the virtually insoluble base at the site of injection, and this reaction retards absorption and thereby does not always give reproducible results. These facts, coupled with the low solubility of the salts of papaverine, have prompted the desire to prepare antispasmodics which would not possess these disadvantages. The chemical modifications designed to bring about these improvements have been concerned (a) with alterations of the aromatic ether groups, (b) with changes at the extracyclic methylene portions of the dimethoxybenzyl group, and (c) with substitution or reduction of the hetero ring.

Systematic replacement of the four methoxyl groups of papaverine by ethoxyls leads to moderately improved alkaloidal drugs, but the tetraethoxy analog, Perparine (XXIII-7), is said to be three times as active, and only one-third to one-half as toxic as papaverine.[3]

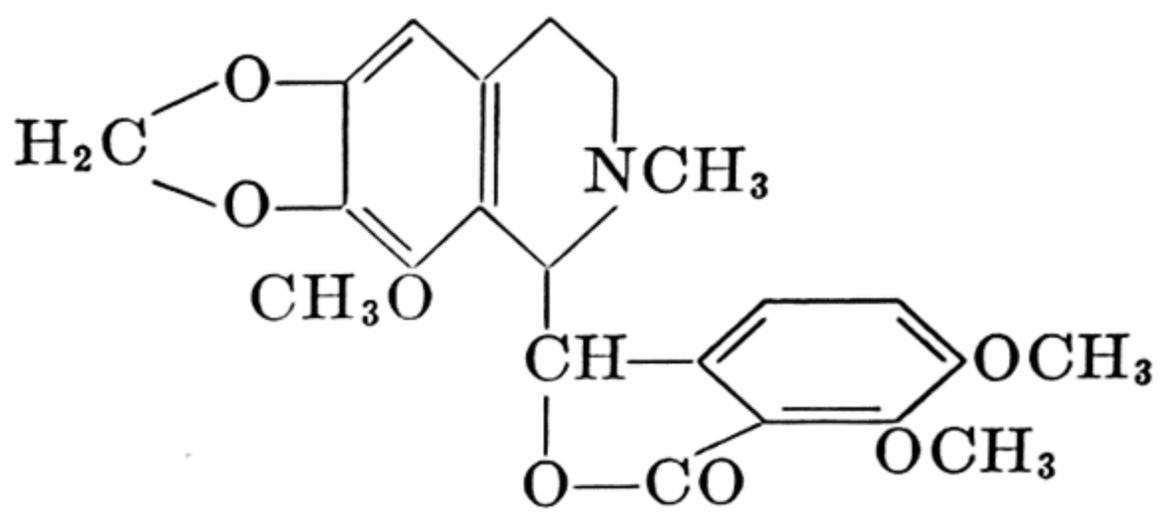


(XXIII-7)

It might be expected that minor changes in the methylene bridge connecting the two ring systems would not seriously affect the pharmacological properties of papaverine. However, papaverinol (XXIII-8) and papaveraldine (XXIII-9) are too toxic to permit much testing in animals. The less closely related opium alkaloid narcotine (XXIII-10) is pharmacologically similar to papaverine but is not used because of its toxic effects.



(XXIII-8): X = CHOH
(XXIII-9): X = CO

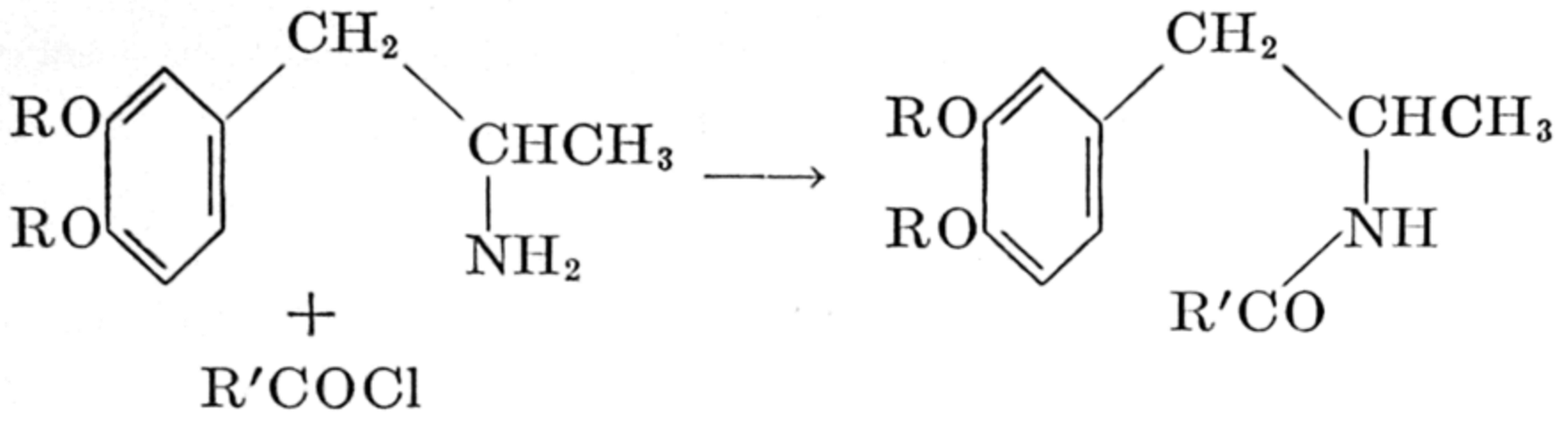


(XXIII-10)

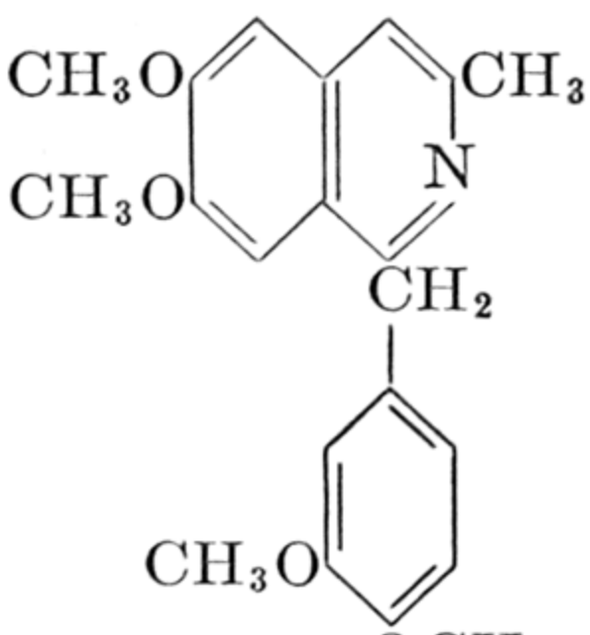
Some of the most effective antispasmodics in the papaverine series have been obtained by substituting position 3 with methyl. Starting with alkoxy substituted β-phenylisopropylamines, such compounds (XXIII-11) can be synthesized by the Bischler-Napieralski isoquinoline synthesis and subsequent dehydrogenation. Of the many variations he tried, Fodor found the 3-methyl homolog of papaverine (XXIII-12) most active.[4] His variations included compounds containing alkyl ether and methylenedioxy groups both in the 3-methylisoquinoline portion and in the benzyl group. In addition, several dialkoxyphenyl ($R' = (RO)_2C_6H_3$-) and dialkoxy-

[3] Issekutz, Leinzinger, and Dirner, *Arch. exptl. Pathol. Pharmakol.*, **164,** 158 (1932). Wolf, French Pat. 719,638 (1932).

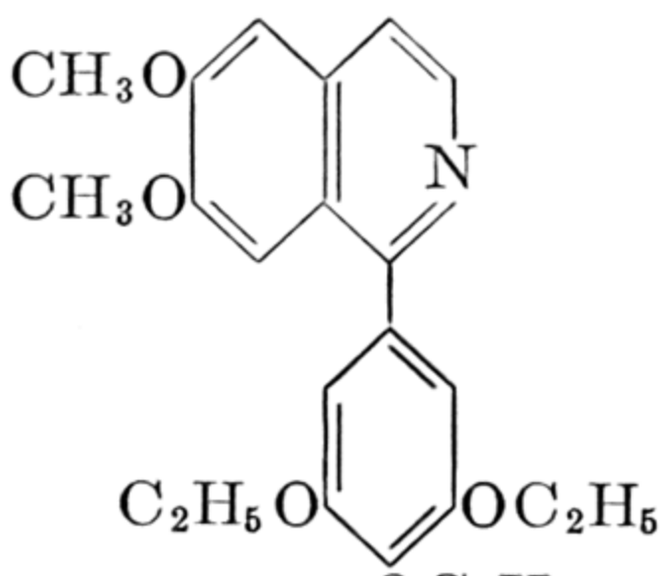
[4] Fodor, *Chem. Abstr.*, **32,** 2124 (1938). Fodor, *Ber.*, **76,** 1216 (1943). Bruckner and Fodor, *Ber.*, **71,** 541 (1938).



(XXIII-11)

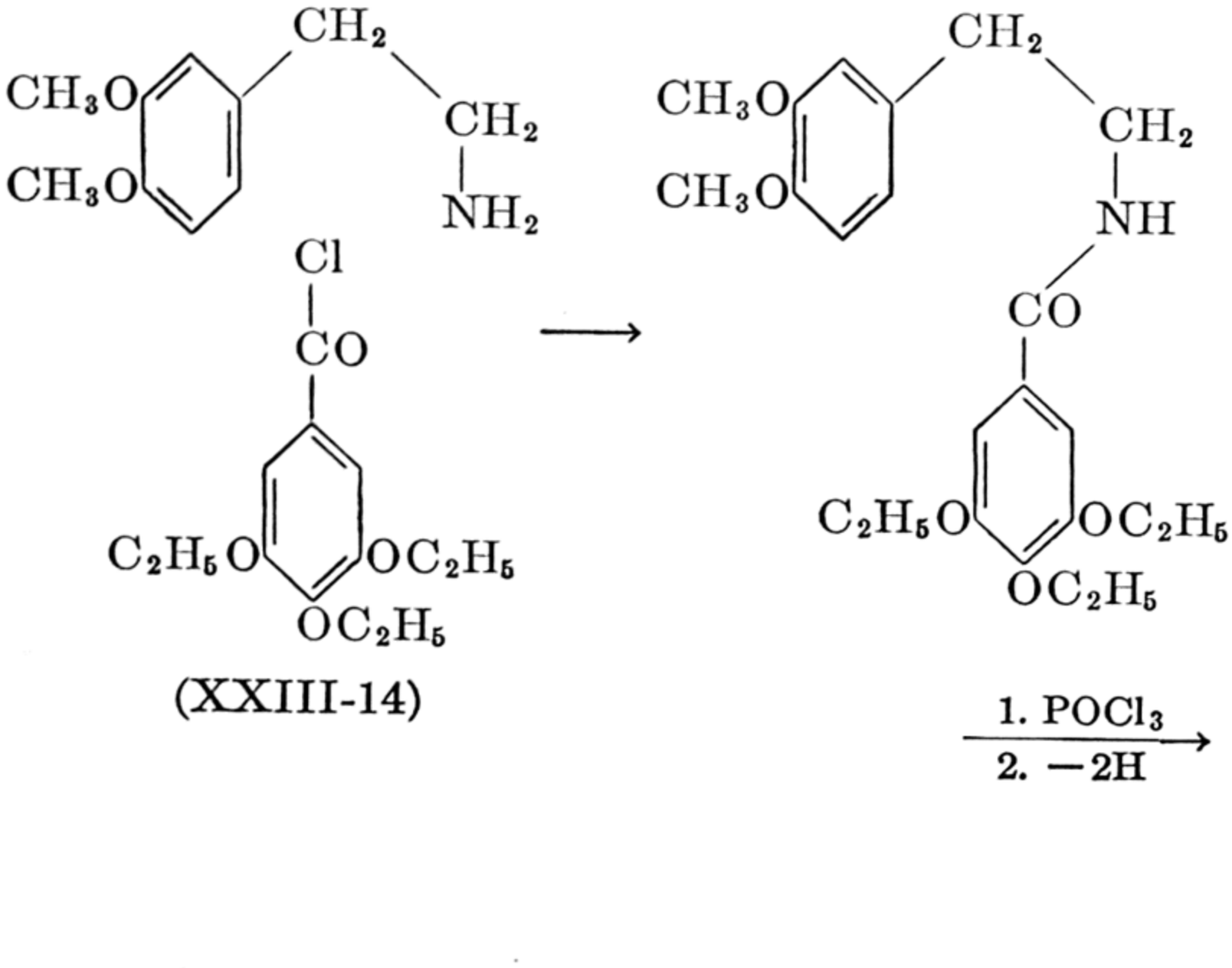


(XXIII-12)



(XXIII-13)

phenethyl ($R' = (RO)_2C_6H_3CH_2CH_2$-) derivatives were tested, and their activity led to the conclusion that the 1-benzyl group was not essential for activity, since several 1-phenyl derivatives were more potent. 6,7-Dimethoxy-1-(3,4,5-triethoxyphenyl) isoquinoline (XXIII-13) used under the name Octaverine, bears out this observation.



(XXIII-14)

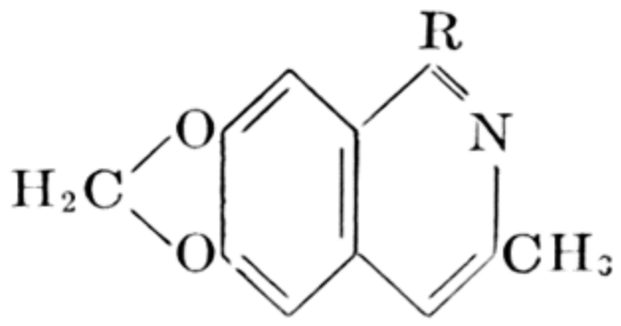
(XXIII-13)

This compound, as well as the trimethoxybenzyl derivative, are accessible from the corresponding ethers of gallic acid (XXIII-14).[5]

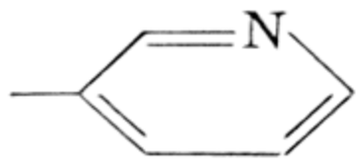
2. Eupaverine

Kreitmair[6] had arrived at similar results when he tested several 3-methyl-6,7-methylenedioxyisoquinoline derivatives (XXIII-14) carrying aryl and aralkyl as well as pyridyl groups in position 1. Table I shows that a simple phenyl or 3-pyridyl group in this position furnishes compounds

TABLE I. PAPAVERINE ANALOGS[7]



(XXIII-14)

R	Spasmolytic Activity	R	Spasmolytic Activity
$-CH_2C_6H_3(OCH_3)_2(3,4)$ (XXIII-1)	1	$-CH_2C_6H_5$	2.5
$-CH_2C_6H_3(O_2CH_2)(3,4)$ (XXIII-16)	2.5	$-C_6H_5$	25
$-C_6H_3(O_2CH_2)(3,4)$ (XXIII-15)	2.5	 (XXIII-17)	20

more than 20 times as potent as papaverine. Two of his compounds which were 2.5 times as active as papaverine had very favorable therapeutic indices and were introduced into therapy as Neupaverine (XXIII-15) and Eupaverine (XXIII-16). Eupaverine has become the most important synthetic papaverine-type drug in Europe.

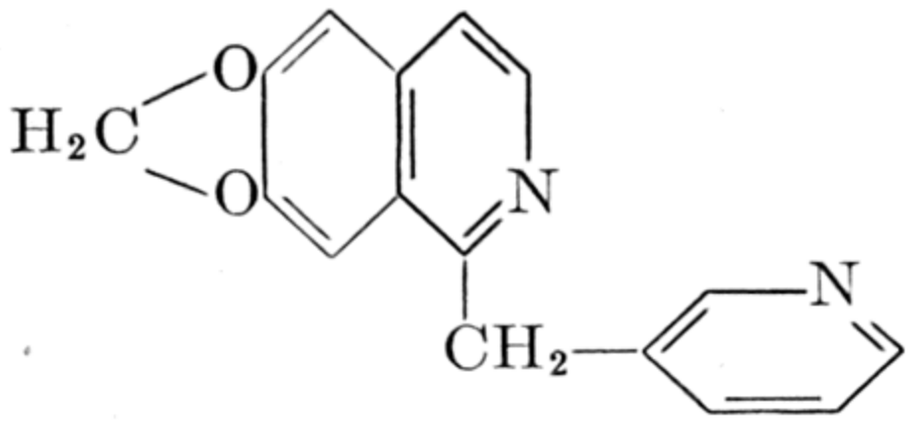
It is interesting to compare the high activity of the pyridine derivative (XXIII-17) with the much lower effect (2 to 5) of the β-picolyl isomer (XXIII-17a).[8]

[5] Slotta, *Angew. Chem.*, **46,** 766 (1933). Chemische Fabrik Asta A. G., French Pat. 760,825 (1934). Ellinger, Koschara, and Seerar, *Klin. Wochschr.*, **13,** 411 (1934).

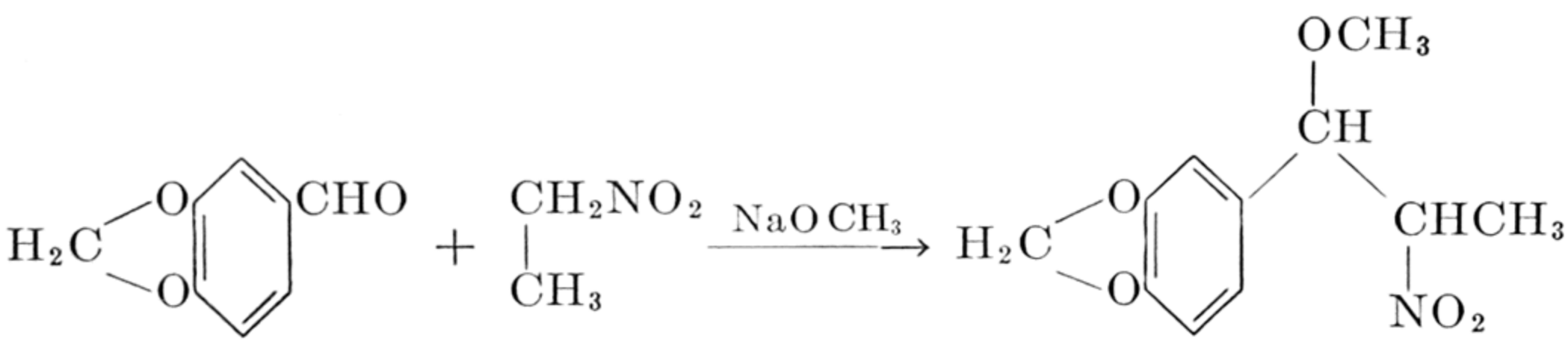
[6] Kreitmair, *Arch. exptl. Pathol. Pharmakol.*, **164,** 509 (1932).

[7] Merck, German Pat. 613,005 (1935).

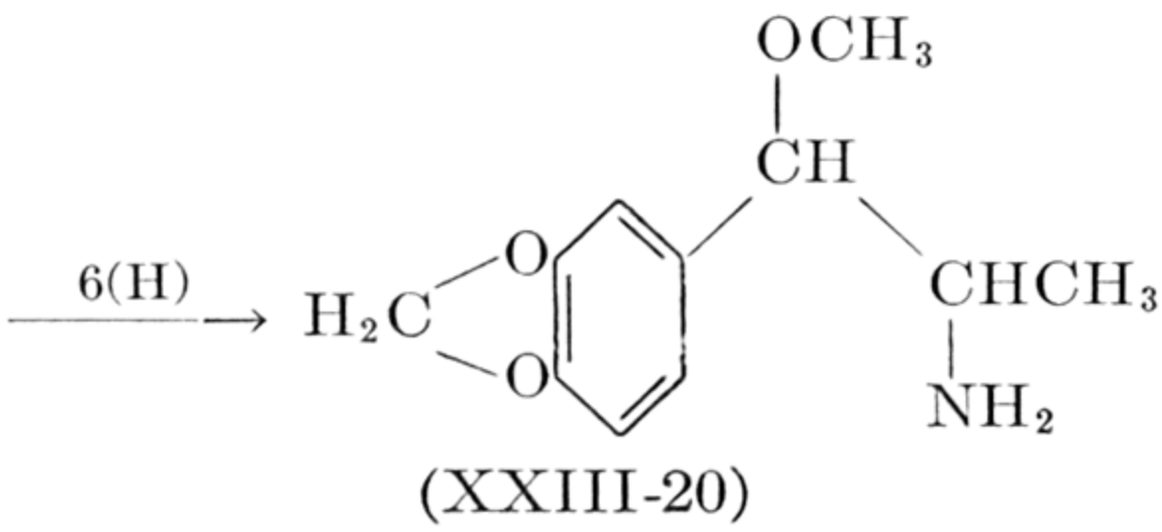
[8] Noller and Azima, *J. Am. Chem. Soc.*, **72,** 17 (1950).



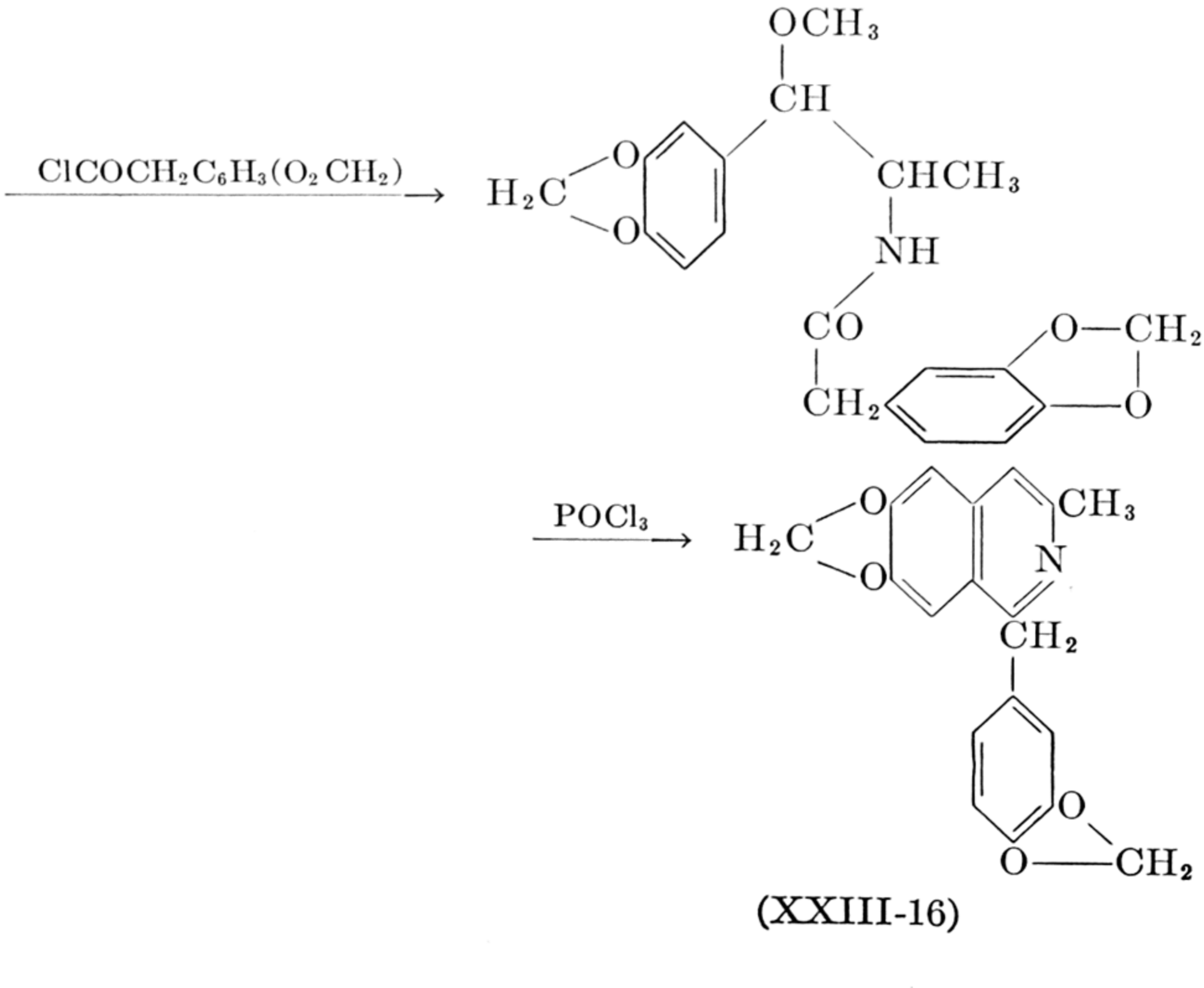
(XXIII-17a)



(XXIII-18) (XXIII-19)



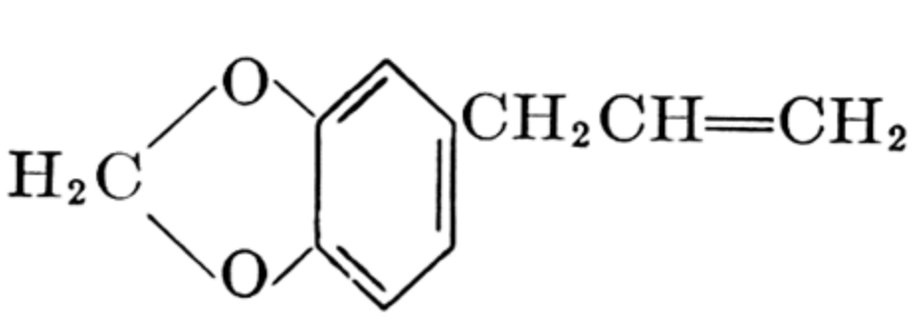
(XXIII-20)



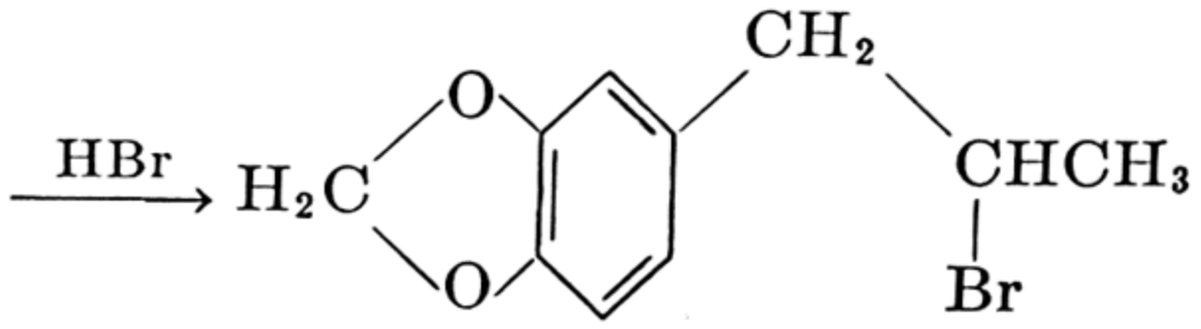
(XXIII-16)

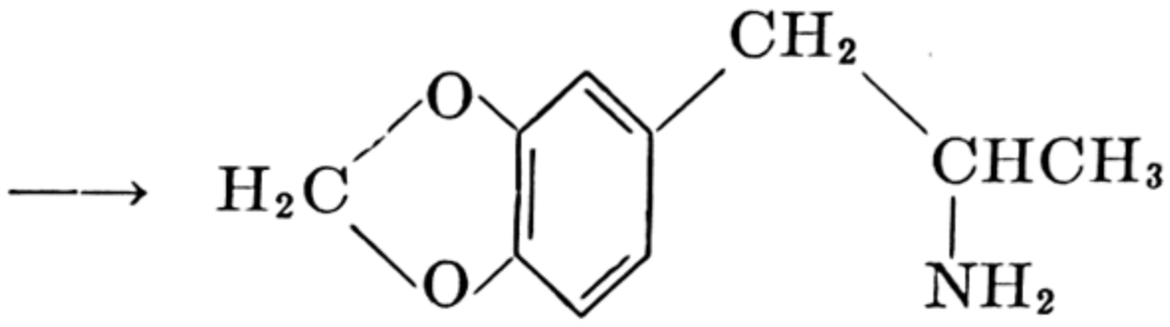
Eupaverine is synthesized[9] by condensing piperonal (XXIII-18) with nitroethane under the influence of sodium methoxide. The nitro ether (XXIII-19) is reduced, and the resulting 1-aryl-1-methoxy-2-methyl-2-aminoethane (XXIII-20) condensed with piperonyl chloride and cyclized with phosphorus oxychloride in toluene solution.

An alternative synthesis follows the standard path of cyclizing a phenethyl phenylacetamide to the corresponding 3,4-dihydroisoquinoline derivative. The amine (XXIII-22) required for synthesizing Eupaverine is obtained readily from safrol (XXIII-21) by adding HBr and aminating.



(XXIII-21)

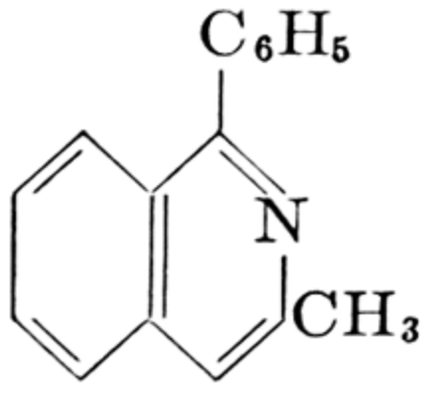




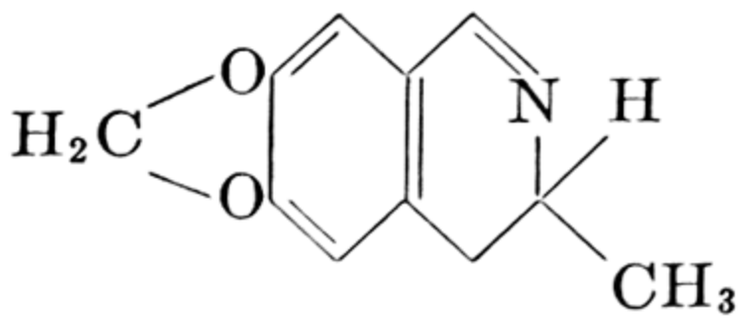
(XXIII-22)

3. Variations of the Hetero-Ring

Omission of the ether groups may not abolish antispasmodic activity (XXIII-23). On the other hand, 1-phenyl-3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (XXIII-24) has no spasmolytic properties but causes an increase in muscle tone instead.

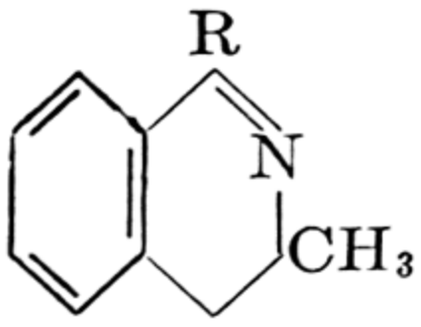


(XXIII-23)

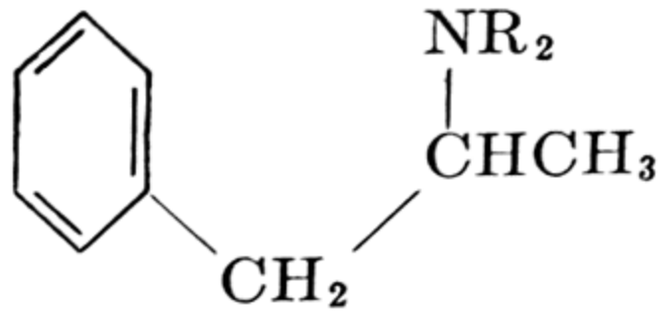


(XXIII-24)

[Activity: 12.5]



(XXIII-25)

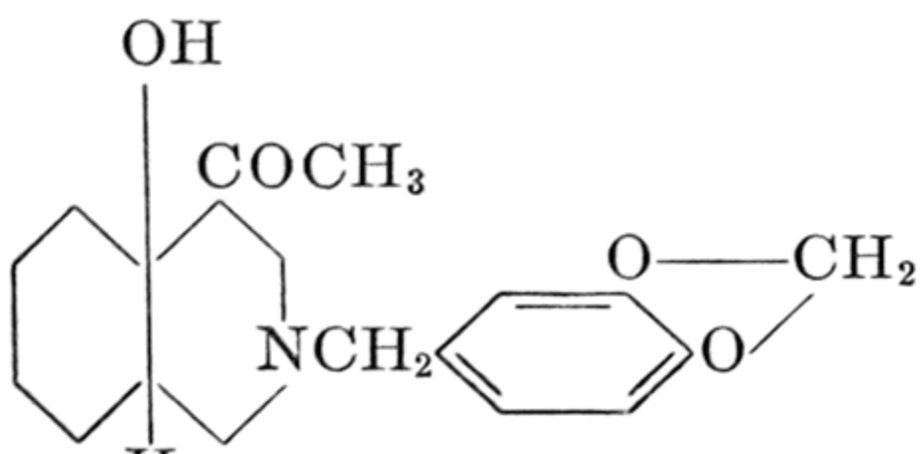


(XXIII-26)

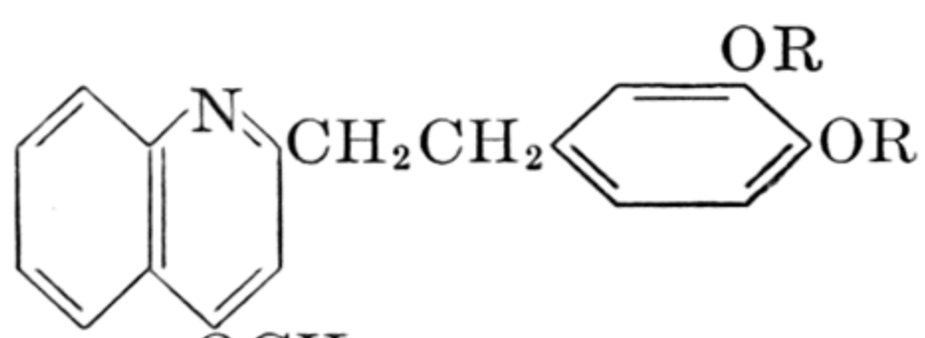
[9] Wolfes and Dobrowsky, German Pat. 556,709 (1932).

The generic relation of 3-methyl substituted 3,4-dihydroisoquinolines (XXIII-25) and of the adrenergic and centrally stimulating β-phenylisopropylamines (XXIII-26) made a closer study of the former type desirable. Several compounds in this series[10] (R = C_6H_5, —$CH_2C_6H_5$, —CH_2CH_2-C_6H_5) relax spasm induced both by acetylcholine and barium chloride. Moreover, they are much less toxic than papaverine in mice. The antispasmodic effect against acetylcholine-induced spasm is unexpected. The other papaverine analogs discussed above are all principally musculotropic in their action; the 3-methyldihydroisoquinolines represent a transition to atropine-type neurotropic compounds.

By condensing 3,4-methylenedioxybenzylamine with two moles of formaldehyde and one mole each of acetone and cyclohexanone, a base of structure (XXIII-27) is formed. This derivative of a fully hydrogenated isoquinoline combines low toxicity with about one-half the antispasmodic activity of papaverine.[11]



(XXIII-27)



(XXIII-28)

R = CH_3: Galipine
$(OR)_2$ = O_2CH_2: Cusparine

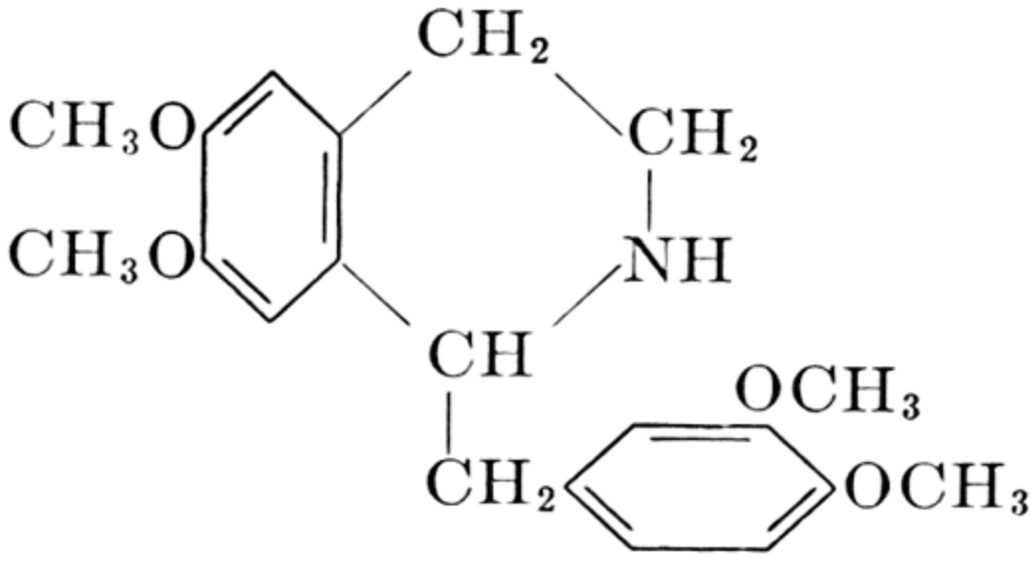
It is questionable whether the isoquinoline ring system is an essential feature of all the antispasmodics in this group. The angostura alkaloids (XXIII-28) which contain a quinoline ring substituted by phenethyl groups in the 2-position, have weak papaverine-like properties.[12] The success of the "open-chain" amines described below lends further credence to that assumption.

IV. ANTISPASMODIC AMINES

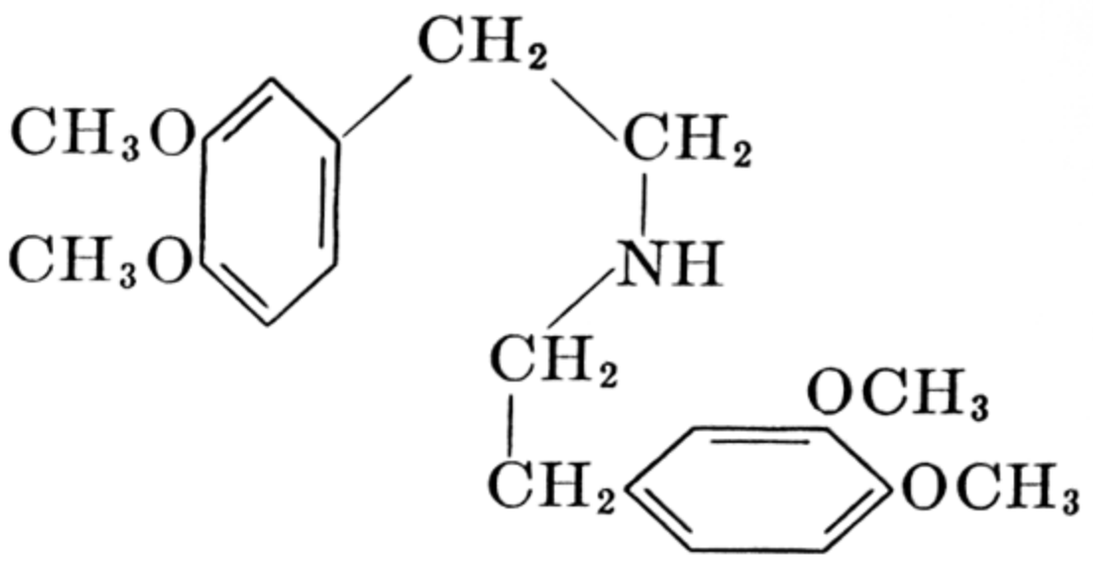
Compounds containing saturated rings often retain their physiological activity if the rings are opened. Tetrahydropapaverine (XXIII-29) acts qualitatively like the parent alkaloid but is weaker in its action. Rosen-

[10] Cunningham and Fellows, *Federation Proc.*, **1,** 148 (1942).
[11] Mannich and Hieronimus, *Ber.*, **75,** 49 (1942).
[12] Krakau, *Kgl. Fysiograf. Sällskap. Lund*, Förh. **15,** 289 (1945); *Chem. Abstr.*, **43,** 3527 i (1949).

mund[13,14] studied the possibility of replacing the tetrahydroisoquinoline nucleus by an open chain. The bis-(dimethoxyphenethyl) amine (XXIII-30) synthesized for this purpose actually exhibited weak antispasmodic properties against experimental spasm precipitated by barium ions. About 140 variations of this structure were carried out, and certain overall regularities became apparent in this series. Di-phenethylamine [$(C_6H_5CH_2CH_2)_2NH$] may serve as a reference material for this discussion.



(XXIII-29)



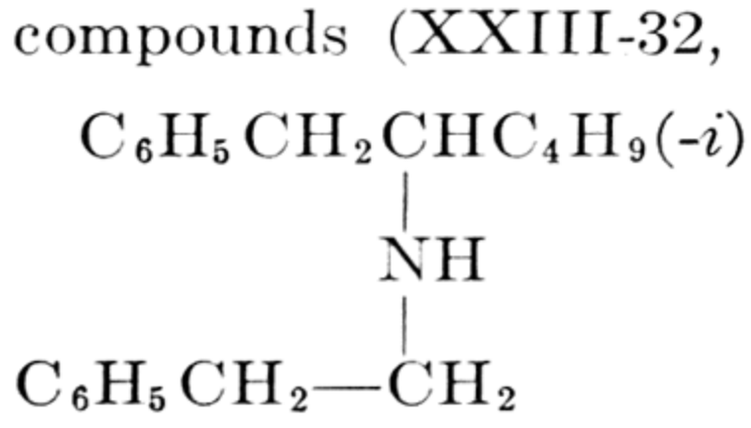
(XXIII-30)

Nuclear alkylation increased antispasmodic activity, and so did N-alkylation except for N-methylation which decreased this property slightly. A significant rise in activity was noted when the aliphatic carbon chain was lengthened, the optimum being reached in bis-(γ-phenylpropyl) ethylamine, $[(C_6H_5CH_2CH_2CH_2)_2NC_2H_5]$ which exhibited 2.3 times the activity of papaverine and was distinguished by its low toxicity. The compound was introduced into clinical use under the name of Sestron (XXIII-31). It may be synthesized[13] by heating γ-phenylpropyl chloride and one-half mole of ethylamine in the presence of KOH at 120° for one day. γ-Phenylpropylethylamine is formed as a by-product of considerably lower boiling point.

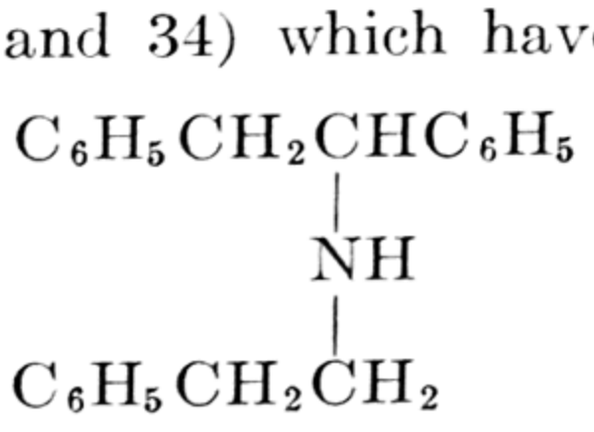
$$C_6H_5(CH_2)_3Cl + C_2H_5NH_2 \xrightarrow{KOH} C_6H_5(CH_2)_3NHC_2H_5 + (C_6H_5CH_2CH_2CH_2)_2NC_2H_5$$

(XXIII-31)

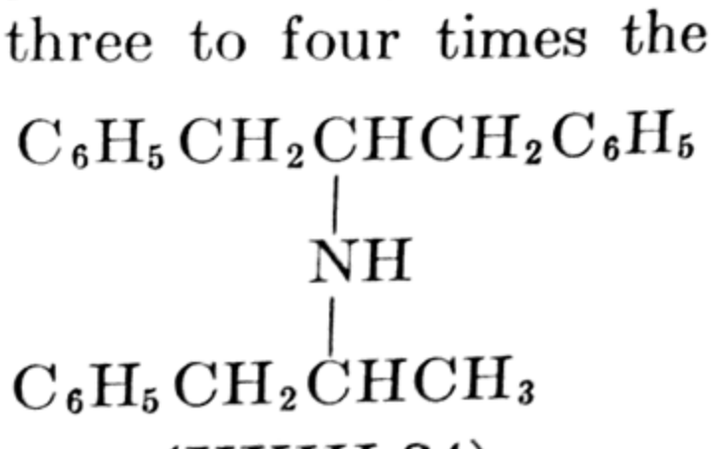
Branching of the carbon chain by alkyl, phenyl or methoxyl produces compounds (XXIII-32, 33 and 34) which have three to four times the



(XXIII-32)



(XXIII-33)



(XXIII-34)

[13] Buth, Külz, and Rosenmund, *Ber.*, **72,** 19 (1939). Külz, Rosenmund, Kayser, Schwarzhaupt, and Sommer, *Ber.*, **72, 2161** (1939).

[14] Külz and Rosenmund, *Klin. Wochschr.*, **17, 345** (1938).

activity of papaverine but the toxicity of these derivatives is increased accordingly.

Similar compounds having tertiary amino groups ($ArCH_2N(CH_3)$-CH_2CH_2Ar) have been found to have valuable antifibrillatory properties.[15]

Other simple aliphatic amines have activities up to almost four times that of papaverine. 2,2,2-Tributylethylamine [$(C_4H_9)_3CCH_2NH_2$] and triamylethylamine [$(C_5H_{11})_3CCH_2NH_2$) represent the optimal compounds in a series of primary aliphatic amines.[16]

Unsaturated and saturated cyclic and aliphatic amines, such as:

$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)NH_2$; $(CH_3)_2CH(CH_2)_3\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2$;



and similar secondary methyl- and allylamines approach papaverine in activity.[17] One compound of this group, Octin (XXIII-35), is said to have a considerably longer duration of action than papaverine, and while its antispasmodic effect is qualitatively similar to that of papaverine, it also exhibits sympathomimetic properties.

$$CH_3CO(CH_2)_2CH{=}C(CH_3)_2 + H_2NCH_3 \longrightarrow CH_3C(=NCH_3)(CH_2)_2CH{=}C(CH_3)_2$$

(XXIII-36)

$$\downarrow$$

$$CH_3\underset{\displaystyle NHCH_3}{\underset{|}{C}}HCH_2CH_2CH{=}C(CH_3)_2$$

(XXIII-35)

Octin is the acid tartrate or hydrochloride of 2-methylamino-6-methylheptene-5. The drug is synthesized by reducing the methylimine of 2-methyl-2-hepten-6-one (XXIII-36) with activated aluminum and alcohol.[18]

Isoamylamino-6-methylheptane (*iso*-$C_5H_{11}NH(CH_2)_5CH(CH_3)_2$) has

[15] Surrey, Mooradian, Cutler, Suter, and Buck, *J. Am. Chem. Soc.*, **71,** 2421 (1949). DiPalma, Lambert, Reiss, and Schults, *J. Pharmacol. Exptl. Therap.*, **98,** 251, 258 (1950).

[16] Junkman, *Arch. exptl. Pathol. Pharmakol.*, **195,** 175 (1940).

[17] Hesse, Niedenzu, and Zeppmeisel, *Klin. Wochschr.*, **15,** 1164 (1936).

[18] Klavehn, German Pat. 617,536 (1935).

been recommended as an effective, rapidly eliminated spasmolytic of low toxicity.[18a]

A series of about 75 alicyclic-aliphatic amines bearing close resemblance to the phenylalkylamines tested by Rosenmund has been reported by Blicke. Some of the most active compounds are listed in Table II.[19] No generalizations about progressive changes of antispasmodic activity in relation to systematic changes in chemical structure were found in this group of compounds, and the introduction of one of them, Cyverine, rested on a purely empirical basis.

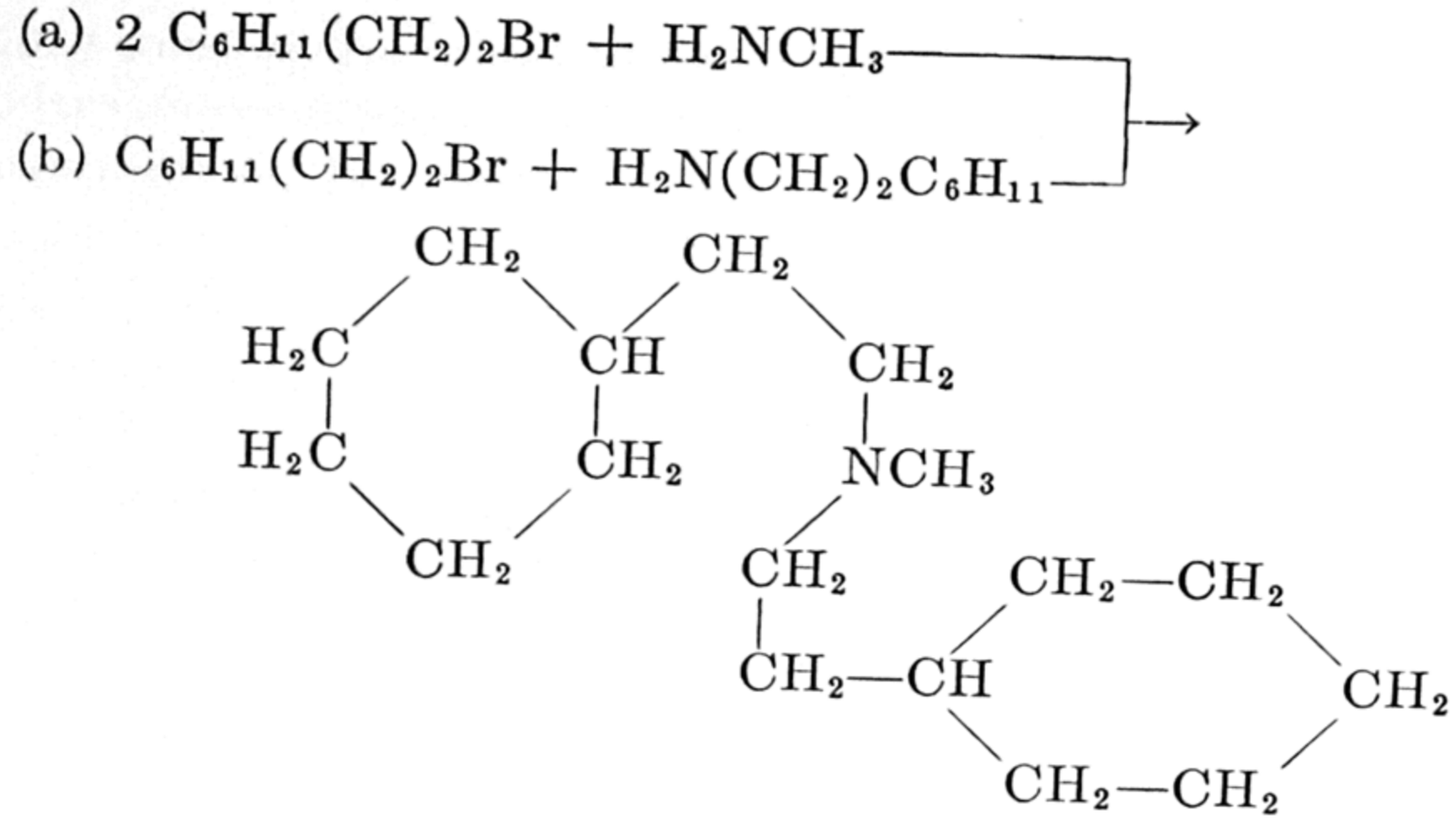
TABLE II. ANTISPASMODIC CYCLOALKYL ALKYLAMINES AND RELATED COMPOUNDS[19]

$C_6H_{11}(CH_2)_4NHC_4H_9$
$C_6H_{11}(CH_2)_2NHR$ ($R=C_4H_9$, C_7H_{15}, C_6H_{11})
$(C_6H_{11}CH_2CH_2)_2NH$
$(C_6H_{11}CH_2CH_2)_2NCH_3$ (Cyverine, XXIII-37)
$C_6H_{11}CH(CH_3)NH(CH_2)_2C_6H_{11}$
$(C_6H_{11}CH_2CH_2)_2NR$ (R = Pr, *i*-Pr)
$(C_5H_9CH_2CH_2)_2NC_5H_{11}$
(3-[or 4-]-$CH_3C_6H_{10}CH_2CH_2)_2NCH_3$
$C_6H_{11}CH_2CH_2N(C_2H_5)CH_2C_6H_{11}$
$C_6H_{11}CH_2CH_2N(C_2H_5)CH_2CH_2C_6H_5$
$[C_6H_{11}CH_2CH_2N(CH_3)CH_2]_2CH_2$
$[C_6H_{11}CH_2CH_2N(CH_3)CH_2]_2$

Cyverine, methyldi-β-cyclohexylethyl-amine (XXIII-37), may be regarded as an alicyclic analog of the 1-benzylisoquinoline alkaloids in which the heterocyclic ring has been ruptured. It has been synthesized by two routes. One (a) utilizes the reaction of β-cyclohexylethyl bromide with methylamine in the presence of sodium carbonate at 150°, while in the other procedure (b) β-cyclohexylethyl bromide and β-cyclohexylethylamine are allowed to react under similar conditions.

The structures of many of these antispasmodic amines bear no little resemblance to those of typical sympathomimetic amines. Several of them do have adrenergic properties as shown in Chapter XIX. No attempt will be made here to include epinephrine, ephedrine, Isuprel and similar potent bronchodilators in this account although these sympathomimetic amines possess powerful antispasmodic properties in asthma. Their mode of action, however, is different from that of the antispasmodics under consideration, in that they stimulate sympathetic nerves, and impose upon the

[18a] Savini, *Arch. int. pharmacodyn. therap.*, **82,** 127 (1950).
[19] Blicke and Monroe, *J. Am. Chem. Soc.*, **61,** 91 (1939). Blicke and Zienty, *J. Am. Chem. Soc.*, **61,** 93, 771 (1939).



(XXIII-37)

parasympathetically constricted vessels a different and often greater relaxation. The true antispasmodics abolish spasm by inhibiting, not by overcompensating, cholinergic stimulation.

V. THE ANTISPASMODIC ESTERS

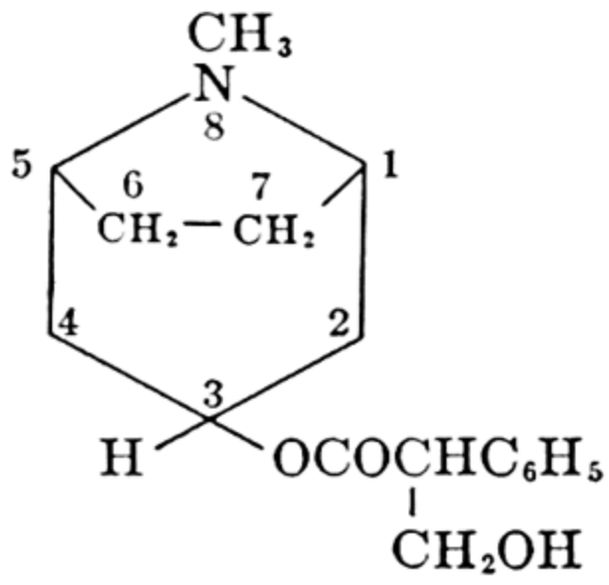
The most valuable antispasmodic property for internal medicine is the inhibition of spasms of smooth muscles which are caused by stimulation of parasympathetic nerves, or by some of the stimulatory effects of acetylcholine. Drugs having this property are exemplified by atropine and its synthetic analogs, esters of basic amino alcohols.

1. Atropine

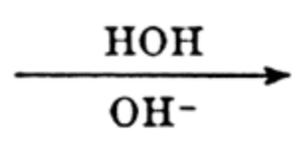
The alkaloid atropine is found in the leaves and roots of the deadly nightshade (*Atropa belladonna*), the thorn apple (*Datura stramonium*), and the henbane (*Hyoscyamus niger*). The high toxicity of the alkaloidal mixture from which atropine is obtained, together with its mydriatic action —it dilates the pupil and paralyzes the accommodation muscles of the eye— have contributed to the name *Atropa belladonna*, the common source of atropine. Atropos was the mythological sybil who cut the thread of life; bella donna is Italian for beautiful lady, as a reminder that women have long used the alkaloidal extract to produce brilliance of the eyes. The name atropine thus implies also the pharmacological dilemma of this drug; the great toxicity and undesirable systemic side-effects severely limit the useful antispasmodic applications of the alkaloid in internal medicine.

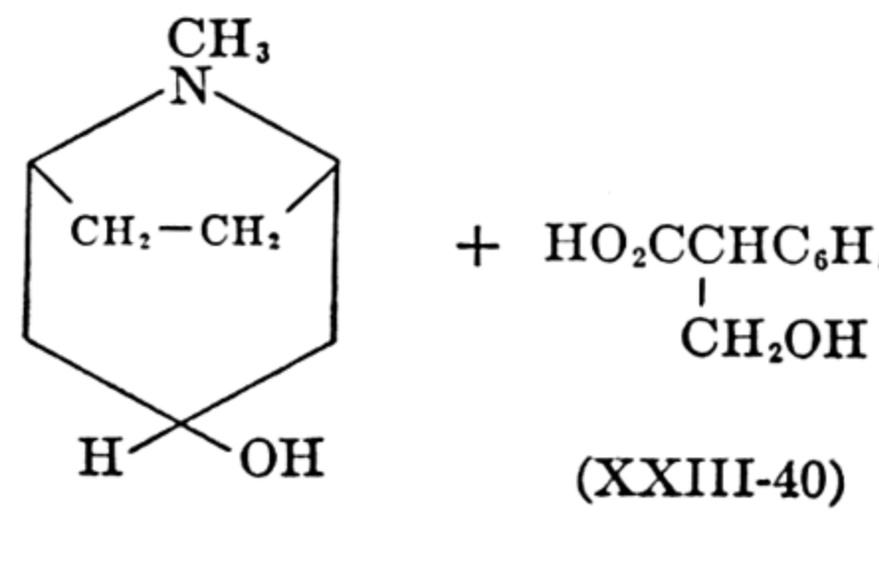
Atropine (XXIII-38) is the tropine (XXIII-39) ester of tropic acid (XXIII-40), and can be hydrolyzed to these components. The alkaloid occurs in the racemic form, accompanied by its more potent but less useful (−)-isomer, hyoscyamine; it is probable that some atropine is racemized

during the extraction process. The only asymmetric carbon atom which makes atropine resolvable resides in tropic acid; the two asymmetric carbon atoms of the tropine moiety in positions 1 and 5 compensate, and the symmetrical molecule of tropine cannot be resolved.



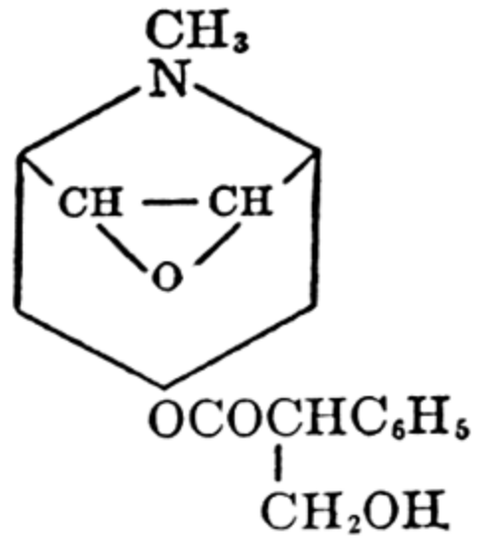
(XXIII-38)





(XXIII-39) (XXIII-40)

Tropine was first synthesized by Willstätter, and later by Robinson and others. The synthesis of tropic acid, and of atropine from its components was achieved by Ladenburg. The reactions involved in these syntheses are classics of alkaloid chemistry, and may be found in standard texts.[20] All of the atropine of commerce is obtained from the crude mixture of atropine and hyoscyamine by racemization with dilute alkali.



(XXIII-41)

Atropine is often accompanied in the plant by the alkaloid scopolamine (XXIII-41), the tropic acid ester of scopine. The latter differs from tropine by an irane ring of which carbons 6 and 7 are part.

Atropine and scopolamine are autonomic blocking agents which abolish all the muscarinic effects of acetylcholine and other cholinergic drugs by acting directly on the effector cells of secretory glands and smooth muscle. Besides these peripheral effects, the belladonna alkaloids stimulate the central nervous system; this action is followed by central depression. Atropine and scopolamine differ in the quality and sites of their central action

[20] Small, in Gilman, *Organic Chemistry*, 2nd ed., Vol. II. Wiley, New York, 1943, pp. 1194–1198.

and lend themselves thereby to different therapeutic applications. Scopolamine has been used to sedate and calm patients suffering from excited states, as a truth serum to obtain confessions from criminals and neurotics, and in the production of twilight sleep in obstetrics in combination with analgetics. Parkinsonism and other paralytic conditions accompanied by tremors can be treated symptomatically with mixtures of atropine and scopolamine.

The toxicity of both alkaloids presents a constant danger in these applications, since their margin of safety is low. Moreover, the peripheral actions of atropine come to the fore, and although they are in themselves useful in certain conditions, they appear as undesirable side-effects when the belladonna bases are employed for medication of the central nervous system.

The peripheral activity of atropine is expressed by preventing involuntary muscles and glands from responding to cholinergic stimulation. Because a complete block of certain parasympathetic responses is achieved, the pharmacodynamically opposed adrenergic impulses are unshackled, and the effect of atropinization resembles often an overactivity of the sympathetic nervous system, or an over-abundance of epinephrine.

In the eye, atropine dilates the pupil (it causes mydriasis) and paralyzes the muscles of accomodation (cycloplegia); these are valuable properties in ophthalmology. The blocking of the stimulation of sweat, salivary and other glands dries up the mucous membranes and surfaces ordinarily kept moist by the excretions from these glands. Likewise, the gastric cells stop producing gastric juice after therapeutic doses of atropine. The alkaloid effectively abolishes intestinal spasm produced by undue parasympathetic stimulation, or as a side-effect of cholinergic drugs such as Prostigmine, Mecholyl, Furmethide or Etamon. Thus, pylorospasm and other intestinal spastic disorders can be improved considerably by the drug. Excessive bed-wetting in children, when caused by spasm of the urinary bladder and vessels, responds well to atropine. Many other spastic conditions lend themselves to treatment with this effective antispasmodic.

Atropine is often administered in small doses together with hypnotics or sedatives designed to improve the mental condition of a patient who worries about a spastic state. The significance of such drug combinations has been discussed in connection with the therapeutic activity of papaverine.

2. Structural Variations

The same procedure of chemical dissection which had led from the tropane alkaloid, cocaine, to Novocaine and its synthetic analogs, has been applied to atropine. The division of the structure into tropine and tropic

acid has facilitated this operation, since each of the two components can be varied over a wide range. Esterification of the different acids and amino alcohols from these experiments has made possible the synthesis of long series of analogs in which small progressive structural changes could be evaluated carefully. The bulk of this work has been carried out during the past fifteen years. The ultimate goal, not yet attained, would be the preparation of a drug which would combine atropine-like activity and potency with the musculotropic features of papaverine.

In approaching permutation of the molecular structure of atropine, two fundamental assumptions were made. First, since tropine itself has no noteworthy spasmolytic activity, it could be regarded functionally as an amino alcohol, and its bicyclic architecture could be looked upon as incidental. While it is true that the esters of many simpler amino alcohols possess antispasmodic properties, the acid portion of these simpler esters had to assume complex proportions in almost all of the more active drugs. It has even been suggested that the roof- or umbrella-like shape of the atropine molecule must be preserved in one or the other section of the amino esters, if not in the alkamine portion then in the acyl moiety. It is too early to say whether these predictions will be borne out by experiments, but no antispasmodic has yet been found which has more than one-half the activity of atropine, especially against intestinal spasm. It may be that powerful antispasmodic action is specifically allied with atropine-like structure from which one cannot deviate without considerable loss of pharmacodynamic action.

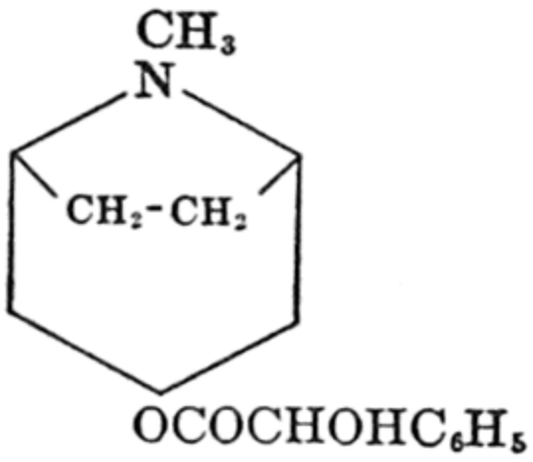
The second assumption in altering the structure of atropine was to consider tropic acid as a branched-chain phenylacetic acid, and to vary the distance between the carboxyl and phenyl groups, as well as the side-chain at the aliphatic position in every conceivable way. Some of these permutations have been restricted to relatively close analogs of tropic acid, but chemical imagination has taken others far afield, and only a superficial relation to tropic acid has been preserved in some of the modifications. It is a tribute to the tedious task of systematic structural alterations that several fairly useful antispasmodics have resulted from these researches.

a. Esters of Tropine

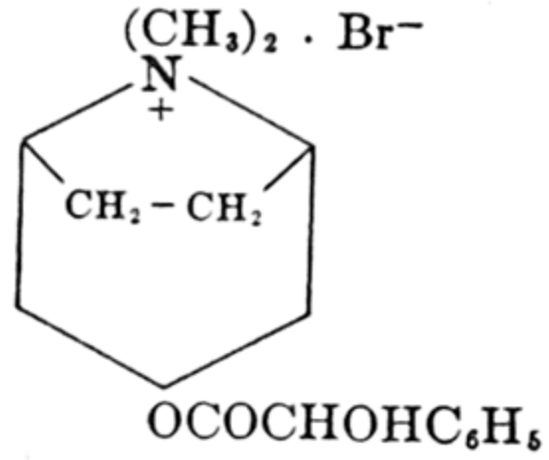
In this group are to be mentioned esters of tropine with acids (tropeines) other than tropic acid, as well as compounds in which the configuration of C^3 of tropine has been reversed (pseudotropine). Several compounds having quaternary nitrogen atoms in the tropine portion also belong here.

The mandelate ester of tropine has been found to be a successful mydriatic and is widely used in ophthalmology under the name of homatropine

(XXIII-42). It is somewhat weaker and less toxic than atropine, and the absence of several of the systemic side-effects of atropine on glands is of particular advantage for local application to the eye. Homatropine is less irritating than atropine, and paralyzes the accomodation muscles for a briefer period than the latter; consequently, normal vision is regained more rapidly, a great advantage after routine ophthalmological measurements.



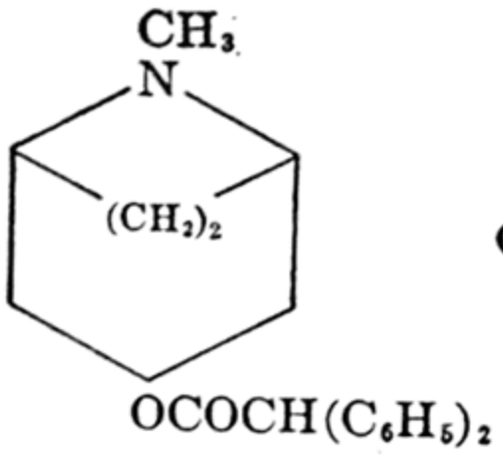
(XXIII-42)



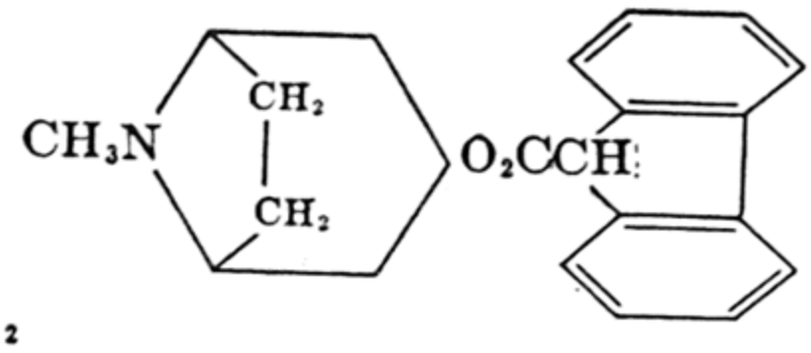
(XXIII-43)

Quaternization of the tertiary nitrogen atom of homatropine furnishes the drug Novatrin (XXIII-43) or homatropine methobromide. Its activity and toxicity are about the same as those of atropine.

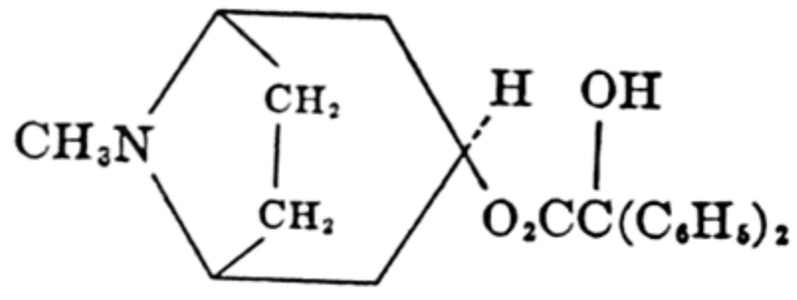
Burtner recently announced the results of tests with esters of tropine and diphenylacetic acid (XXIII-44) and fluorene-9-carboxylic acid (XXIII-45). They are said to be one-fourteenth as active as atropine, and one-half as active as papaverine. Such drugs, if sufficiently non-toxic, would approach the properties of a very desirable antispasmodic.[21]



(XXIII-44)



(XXIII-45)



(XXIII-46)

The diphenylglyoxylate of pseudotropine (XXIII-46) is much less active and more toxic than atropine.[22]

The quaternary methonitrate of atropine is known as Eumydrine, and atropine-N-oxide as Genatropine. Both drugs have been tried as mydriatics.

[21] see also Miescher and Hoffman, U. S. Pat. 2,143,491 (1939).
[22] Kreitmair, *Klin. Wochschr.*, **15,** 676 (1936).

b. Amino Alkyl Esters of Tropic Acid

Working with synthetic DL-tropic acid, some of the early investigators in this field attempted to prepare suitable antispasmodics. Diethylaminoethyl tropate (XXIII-47) is about one seventh as active as atropine, and one twentieth as potent as papaverine.[23] The only compound in this series which has been used clinically is Syntropan (XXIII-48) but although its toxicity is relatively low, its potency is also of a minor order.[24]

$$(C_2H_5)_2NCH_2CH_2O_2CCH(CH_2OH)C_6H_5$$

(XXIII-47)

$$(C_2H_5)_2NCH_2C(CH_3)_2CH_2O_2CCH(CH_2OH)C_6H_5$$

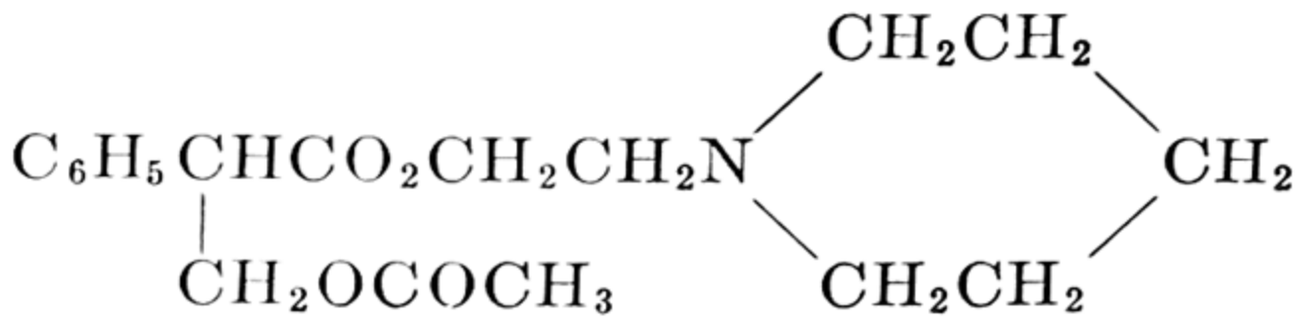
(XXIII-48)

$$C_6H_5CHCO_2CH_2C(CH_3)_2CH_2N^+(C_2H_5)_3\cdot Br^-$$
$$\quad\quad|$$
$$\quad CH_2OCOCH_3$$

(XXIII-49)

Acetylation of the primary alcohol group of tropic acid seems to have a beneficial effect on neurotropic activity. The compound corresponding to Syntropan, having a quaternary nitrogen atom (XXIII-49), has one-half the activity of atropine.

The drug Navigan is β-piperidinoethyl acetyltropate (XXIII-50); it inhibits completely contractions of the rabbit intestine caused by pilocarpine and acetylcholine in a dilution of 1:300,000.[25] Like other esters in this group, it is used mainly as a mydriatic agent.



(XXIII-50)

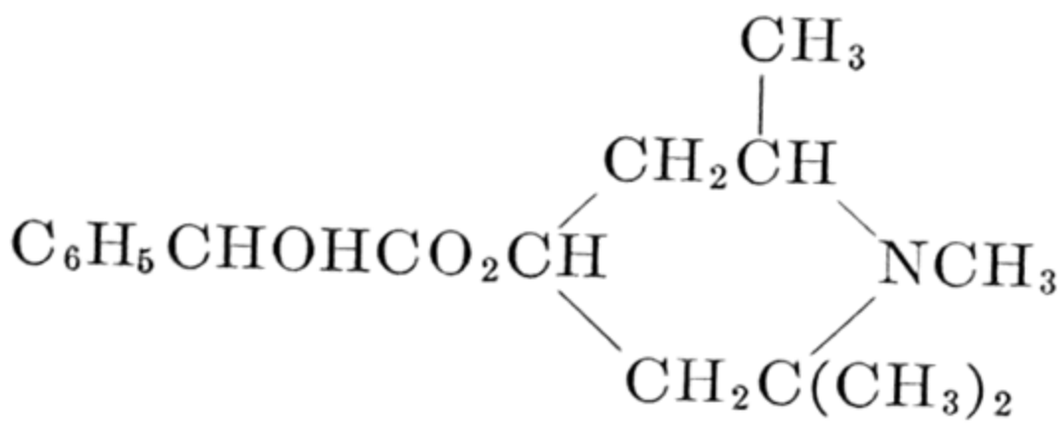
Etherification of the —CH_2OH group of tropic acid, or dehydration to α-phenylacrylic acid, $C_6H_5C(=CH_2)COOH$, produces acid moieties from which neurotropically weakly active aminoalkyl esters can be derived. However, the papaverine-type action is slightly increased, an indication, that omission of the alcoholic hydroxyl group can lead to qualitatively altered antispasmodics.

[23] Burtner and Cusic, *J. Am. Chem. Soc.*, **65,** 262 (1943).
[24] Fromherz, *Arch. exptl. Path. Pharmakol.*, **173,** 86 (1933).
[25] Toda, *Arch. exptl. Path. Pharmakol.*, **146,** 313 (1929).

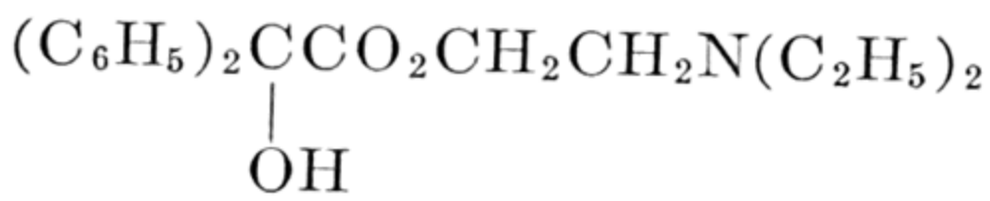
c. Esters of other Hydroxy Acids

Basic esters of mandelic, and of benzilic acid have been studied most widely in this series. The preparation of such compounds used to be complicated because the most profitable mode of esterification, treatment of the amino alcohols with acid chlorides, was not applicable to acids containing alcoholic hydroxyl groups. This difficulty has been overcome recently by a base catalyzed method of alcoholysis. The readily accessible ethyl esters of the hydroxy acids are heated with amino alcohols in the presence of catalytically small amounts of sodium alkoxides.[26]

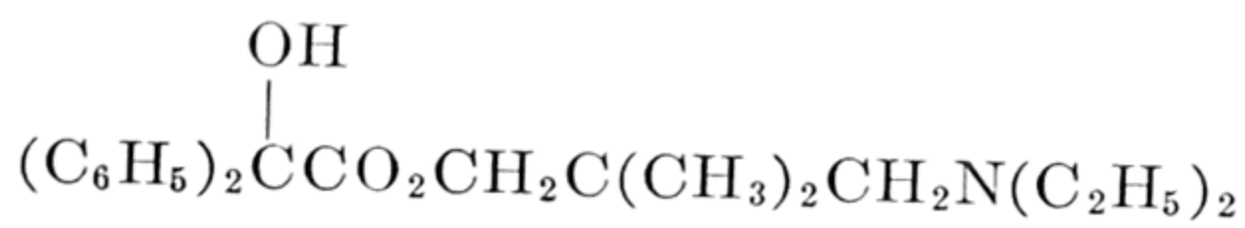
On the whole, the basic esters of mandelic acid are too ineffective to be of practical use, although one of them, Eucatropine (Euphthalmine, XXIII-51), is used as a mydriatic. Much more attention has been paid to esters of



(XXIII-51)



(XXIII-52)



(XXIII-53)

benzilic acid, some of which are as active as atropine against acetylcholine induced experimental spasm. Diethylaminoethyl benzilate (XXIII-52) is 1.4 times as active as papaverine; a more complex ester (XXIII-53) is as active as atropine but also twelve times as toxic.

d. Aminoalkyl Esters of Aryl Aliphatic Acids

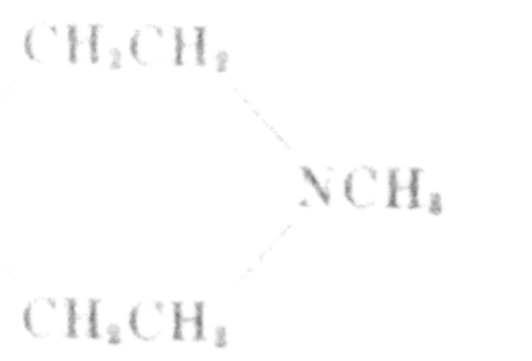
Many hundreds of compounds of this general structure have been studied as potential antispasmodics, following the lead that β-diethylaminoethyl diphenylacetate (Trasentin, XXIII-54) possessed both atropinic and papaverine-like activity,[27] although only to a modest extent. This was one of the early examples of musculotropic action in a basic ester, and started the search for more potent drugs in this series.

[26] Holmes, U. S. Pat. 2,399,736 (1946). Hill and Holmes, U. S. Pat. 2,394,770 (1946); *J. Am. Chem. Soc.*, **71,** 642 (1949).

[27] Meier, *Klin. Wochschr.*, **15,** 1403 (1936).

TABLE III. ANTISPASMODIC ACTION OF AMINO ALCOHOL ESTERS OF ARYLALIPHATIC ACIDS

RR'R''CO$_2$R'''

R	R'	R''	R'''	Ac. Ch.[a]	Ba[a]	H[a]	Reference
Atropine LD_{50} (subcutaneously) 500–700 mg./kg.				100	2.5–5	25	
Papaverine LD_{50} (subcutaneously) 300–400 mg./kg.				1–1.4	100	100	
C_6H_5	C_6H_5	H	$CH_2CH_2NEt_2$	20	80		31
C_6H_5	C_6H_5	H	$CH_2CH_2NEt_2$	5	66	66	32 (Trasentin)
C_6H_5	C_6H_5	H				100	33
C_6H_5	C_6H_5	H	$CH_2C(CH_3)_2CH_2NC_4H_8O$			200	33
C_6H_5	C_6H_5	H		8.3	100	200	34
C_6H_5	C_6H_5	OH	$CH_2CH_2NEt_2$	20	142	20	34
C_6H_5	C_6H_5	Cl	$CH_2CH_2NEt_2$	20	142	66	34
n-$C_5H_{11}C_6H_4$	C_6H_5	OH	$(CH_2)_2NEt_2$	20	140	20	20

R	R′	R″	R‴	Ac. Ch.[28]	Ba[29]	Hi[30]	Reference
C_6H_5	$C_6H_5CH_2$	H	$(CH_2)_2NEt_2$	2	250	500	32
$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	H	$(CH_2)_2NEt_2$	0.1	300		32
$C_6H_5CH_2$	*i*-C_3H_7	H	$(CH_2)_2NEt_2$	0.16	150	600	32
cyclo-C_6H_{11}	C_6H_5	H	$(CH_2)_2NEt_2$	90	90		35 (Trasentin-H)
" C_6H_{11}	$(C_2H_5)_2N(CH_2)_2C_6H_4$	H	$(CH_2)_2NEt_2$	110	110		35
2-Thienyl	1-Naphthyl	OH	$(CH_2)_2NEt_2$	40	250		36
"	C_6H_5	OH	$(CH_2)_2NEt_2$	120	100		36
"	C_6H_5	OH	$(CH_2)_3NEt_2$	100	100		36
"	C_6H_5	OH	$(CH_2)_2NC_5H_{10}$	40	200		36
"	*cyclo*-C_6H_{11}	OH	$(CH_2)_2NEt_2$	160	250		36
				400			37
"	"	OH	$(CH_2)_3NEt_2$	160	500		36
"	"	OH	$(CH_2)_2NC_5H_{10}$	140	100		36
"	2-Thienyl	H	$(CH_2)_2NC_5H_{10}$	20	100		36
"	$C_6H_5CH_2$	H	$(CH_2)_3NEt_2$	40	50		36

[28] Ac. Ch.: Inhibition of spasm caused by acetylcholine. Figures refer to the relative activity of atropine taken as 100.
[29] Ba: Inhibition of spasm caused by barium ions. Figures refer to the relative activity of papaverine taken as 100.
[30] Hi: Inhibition of spasm caused by histamine. Figures refer to activity of papaverine taken as 100; where figures are set between the Ba and Hi columns, the experimenter has given only figures expressed as "papaverine activity."

$(C_6H_5)_2CHCO_2CH_2CH_2N(C_2H_5)_2$

(XXIII-34)

Table III lists some of the principal types of compounds in the category under discussion. In the thiophene analogs of benzilate esters, the goal of combining the activity of both alkaloids has been achieved in several cases.[*] It should be remembered, however, that the therapeutic ratio of a compound, and not its activity alone, determines its therapeutic usefulness. Thus no suitable drug fulfilling all medicinal requirements of an anticholinergic has yet been found even among these highly active compounds, which has stimulated and widespread efforts to find improved

[illegible] esters of benzilic acids or their heterocyclic analogs [illegible] than those of the corresponding non-alkyl [illegible] esters of benzilic acids have a greater tendency [illegible] It has been proposed that the amino alcohol [illegible] and the acid portion the potency of the actum.[**] [illegible] and unsubstituted derivatives usually make for [illegible] like compounds.

[illegible] benzilic acid may illustrate further these [illegible] (XXIII-35) has been found the quaternary ammonium [illegible] (XXIII-36) has been found to possess a [illegible] the atropine type.[*]

[illegible]

(XXIII-36)

[illegible] tertiary [illegible] It [illegible] excellent

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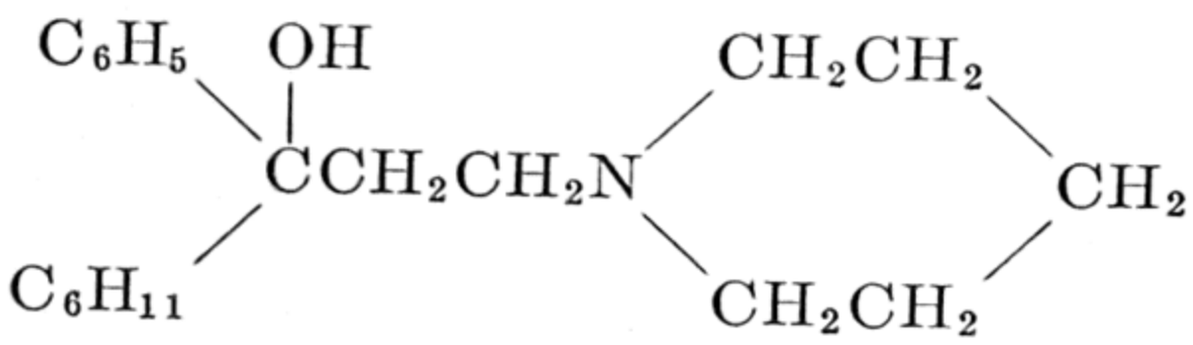
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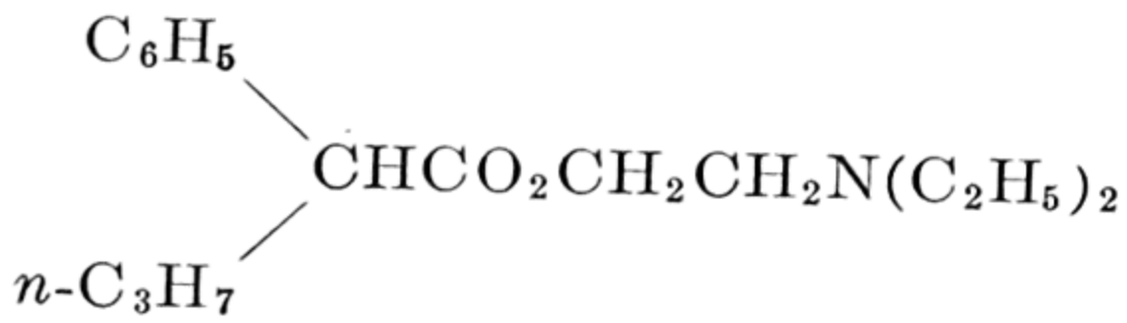
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[illegible] 85, 45 (1945).

therapeutic properties in Parkinsonism (paralysis agitans) which is seen as a frequent sequel to the virus-caused lethargic encephalitis (epidemic sleeping sickness). The drug has become known under the name of Artane or trihexyphenidyl (XXIII-57).[42]

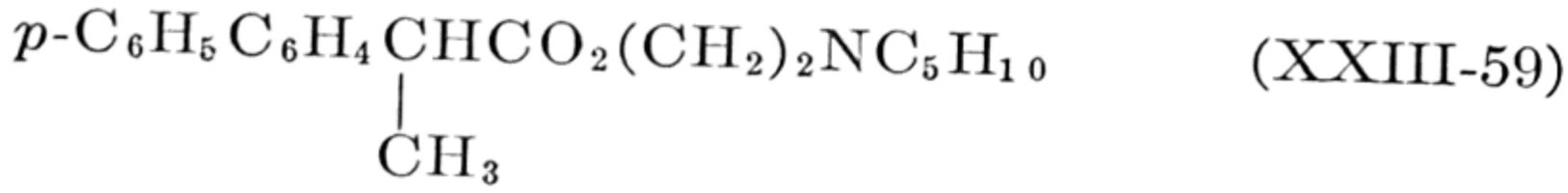


(XXIII-57)

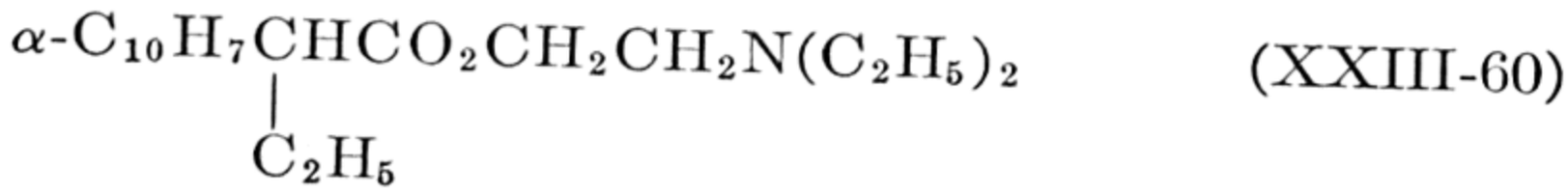


(XXIII-58)

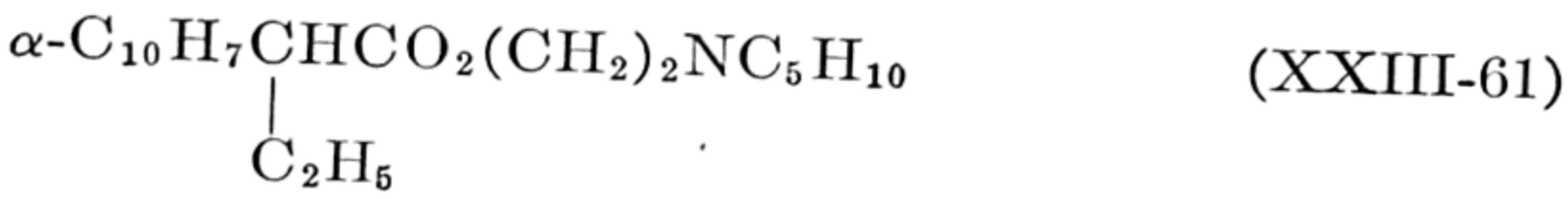
Esters of simple aliphatic acids do not exhibit antispasmodic activity unless the acid contains at least six carbon atoms. Substitution of the aromatic nuclei of diphenylacetic acid derivatives by nitro or amino groups abolishes activity. In the series of α-phenylaliphatic acids ($R = C_6H_5$, $R' =$ alkyl), α-phenylvaleric acid presented the optimum acid portion for spasmolytic activity. The diethylaminoethyl ester of this acid is known as Propivan (XXIII-58).



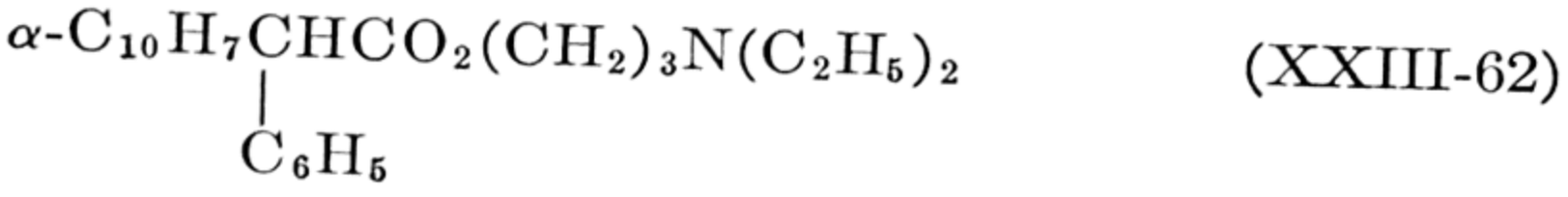
(XXIII-59)



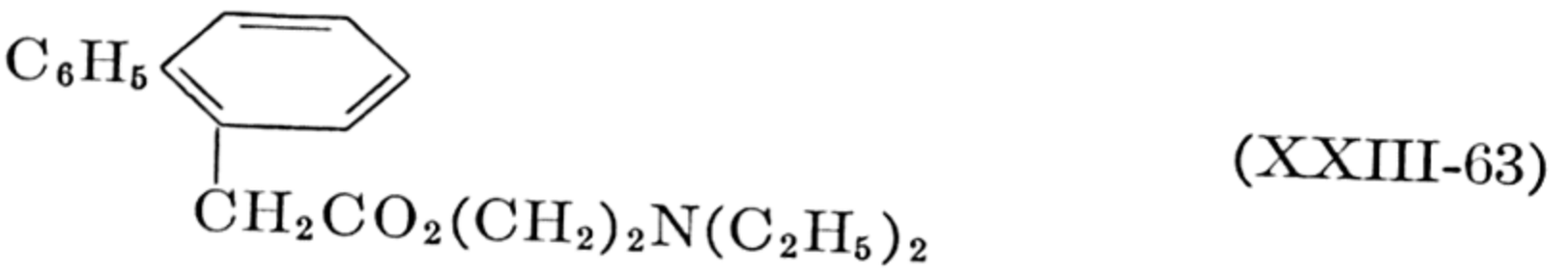
(XXIII-60)



(XXIII-61)



(XXIII-62)

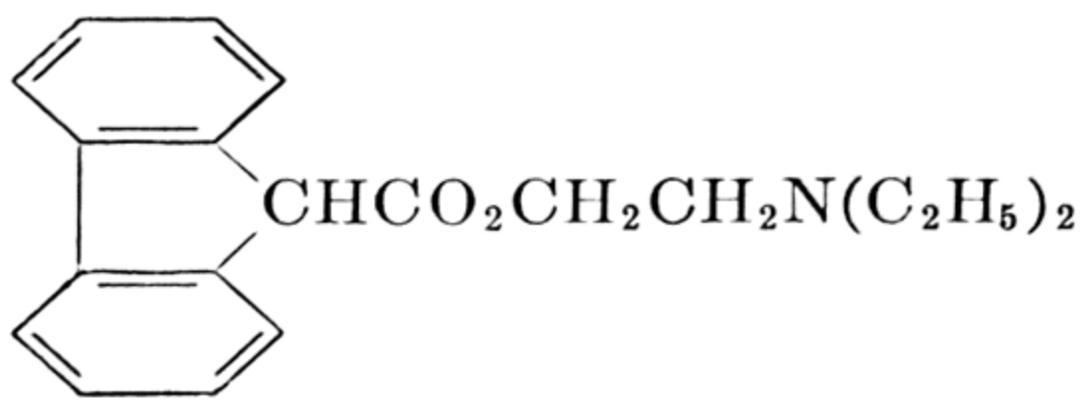


(XXIII-63)

[42] Corbin, *J. Am. Med. Assoc.*, **141,** 377 (1949). Doshay and Constable, *ibid.*, **140,** 1317 (1949).

Variations of the structure of di- and trisubstituted acetic acids were performed by remaining within the approximate range of the molecular weight of esters of diphenylacetic acid but concentrating the bulk of the weight in one substituent. Examples were the four esters of α-(*p*-xenyl-propionic (XXIII-59) and substituted α-naphthylacetic acids (XXIII-60, XXIII-61, and 62) which had atropine activities of 2 to 10 (atropine = 100).[43] On the other hand, the *o*-biphenylacetic acid derivative (XXIII-63) possessed an activity equal to papaverine while its atropine-like action was negligible.[44]

An interesting "bio-isosteric" modification of the structure of diphenylacetic was proposed by Burtner and Cusic.[45] By joining the *o*-positions of the two phenyl groups, fluorene-9-carboxylic acid can be designed; many dialkylaminoalkyl esters of this acid exhibit up to 14% of the action of atropine on acetylcholine induced spasm, and up to 166% of the effect of papaverine on histamine-produced spasm. The pharmacologically optimal drug of this series is diethylaminoethyl fluorene-9-carboxylate which is used under the clinical name of Pavatrine (XXIII-64).



(XXIII-64)

The idea of linking the two phenyl groups at the *ortho* positions can be varied in many ways. Typical examples are 9, 10-dihydroanthracene-9-carboxylic acid, dibenzopyran-10-carboxylic acid, dibenzothiapyran-10-carboxylic acid, and 5-methyl-*meso*-dihydroacridine-10-carboxylic acid. A few basic esters of these acids are listed in Table IV.

A fairly constant correlation of papaverine-type (myotropic) antispasmodic activity with local anesthetic action was observed among these compounds.[46] On the other hand, atropine-like activity shows no relation to local anesthetic potency. The properties of atropine fit into this scheme, since atropine barely has any local anesthetic action. This contrasts with cocaine which contains, as the most pronounced structural alteration, a

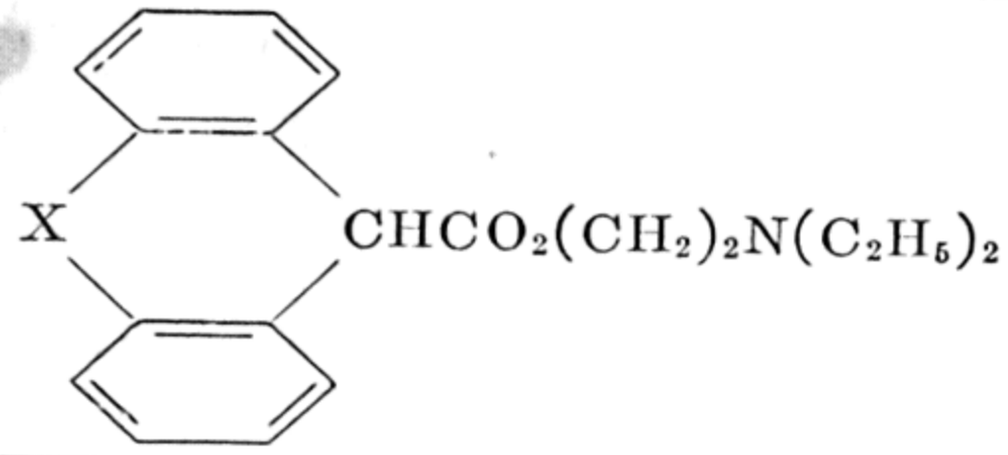
[43] Blicke and Grier, *J. Am. Chem. Soc.*, **65,** 1725 (1943). Lewis, Lands, and Geiter, *Federation Proc.*, **2,** 29 (1943). Blicke and Feldkamp, *J. Am. Chem. Soc.*, **66,** 1087 (1944).

[44] Burtner and Cusic, *J. Am. Chem. Soc.*, **65,** 1582 (1943).

[45] Burtner and Cusic, *J. Am. Chem. Soc.*, **65,** 262, 1582 (1943). Compare Hromatka, U. S. Pat. 2,221,828 (1940).

[46] Lehmann and Knoefel, *J. Pharmacol. Exptl. Therap.*, **74,** 274 (1942).

TABLE IV. BASIC ESTERS OF POLYNUCLEAR CARBOXYLIC ACIDS[45]



	Ac. Ch. (Atropine = 100)	Hi (Papaverine = 100
X = CH_2	2.8	2000
X = CH_3CH	2.8	1000
X = O	28	250
X = S	2.3	300
X = CH_3N	0.35	100

carbomethoxy group in the tropane nucleus. Cocaine is virtually devoid of antispasmodic activity.

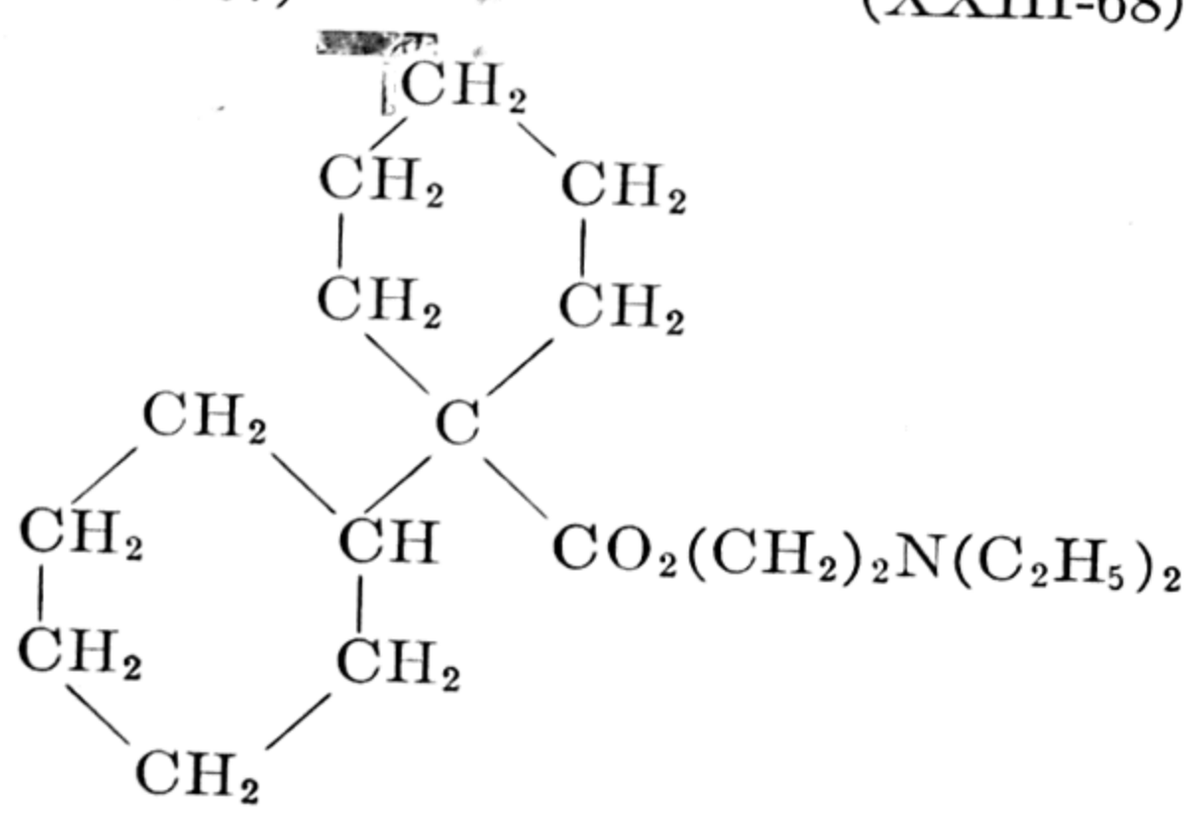
The anticholinergic activity of dialkylaminoalkyl esters of cycloaliphatic acids in which the cyclic radical is separated from the ester group by one or more aliphatic carbon atoms[47] [cyclic R-$(CH_2)_{1,2}$-$CHRCO_2CH_2CH_2NEt_2$] is low in comparison with esters of the structure [cyclic-R-$CHRCO_2CH_2$-CH_2NEt_2]. This is also borne out by the observation that isosteric replacement of the methylene group of dibenzylacetic acid esters (XXIII-

$(C_6H_5CH_2)_2CHCO_2(CH_2)_2N(C_2H_5)_2$
(XXIII-65)[49]

$(C_6H_5O)_2CHCO_2(CH_2)_2N(C_2H_5)_2$
(XXIII-66)[50]

$ArOCHRCO_2(CH_2)_nNR_2$
(XXIII-67)

$ArOCHRCONH(CH_2)_nNR_2$
(XXIII-68)

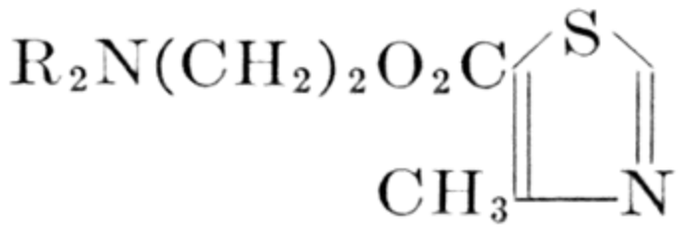


(XXIII-68a)

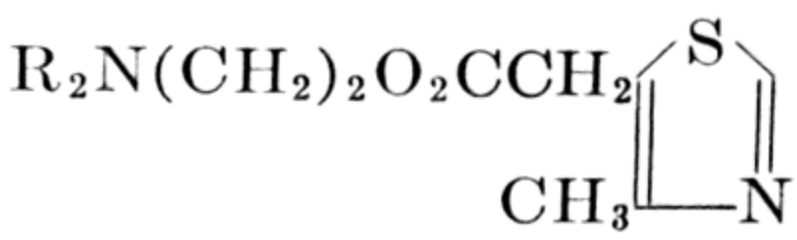
[47] Blicke and Leonard, *J. Am. Chem. Soc.*, **68,** 1934 (1946).

65)[49] by oxygen leads to dialkylaminoalkyl diphenoxyacetates (XXIII-66) of very low potency.[50] Dialkylaminoalkyl esters (XXIII-67) and amides (XXIII-68) of α-phenoxyaliphatic acids have been claimed as antispasmodics and analgetics.[48] Recently, β-diethylaminoethyl-1-cyclohexylcyclohexanecarboxylate (Bentyl, XXIII-68a) has been shown to be one-tenth as active as atropine against acetylcholine-produced spasm.

A comparison of basic esters of thiazolecarboxylic (XXIII-69) and thiazoleacetic acids (XXIII-70) indicates that the compounds having the ester function directly attached to the thiazole ring are superior to the more aliphatic derivatives.[51]

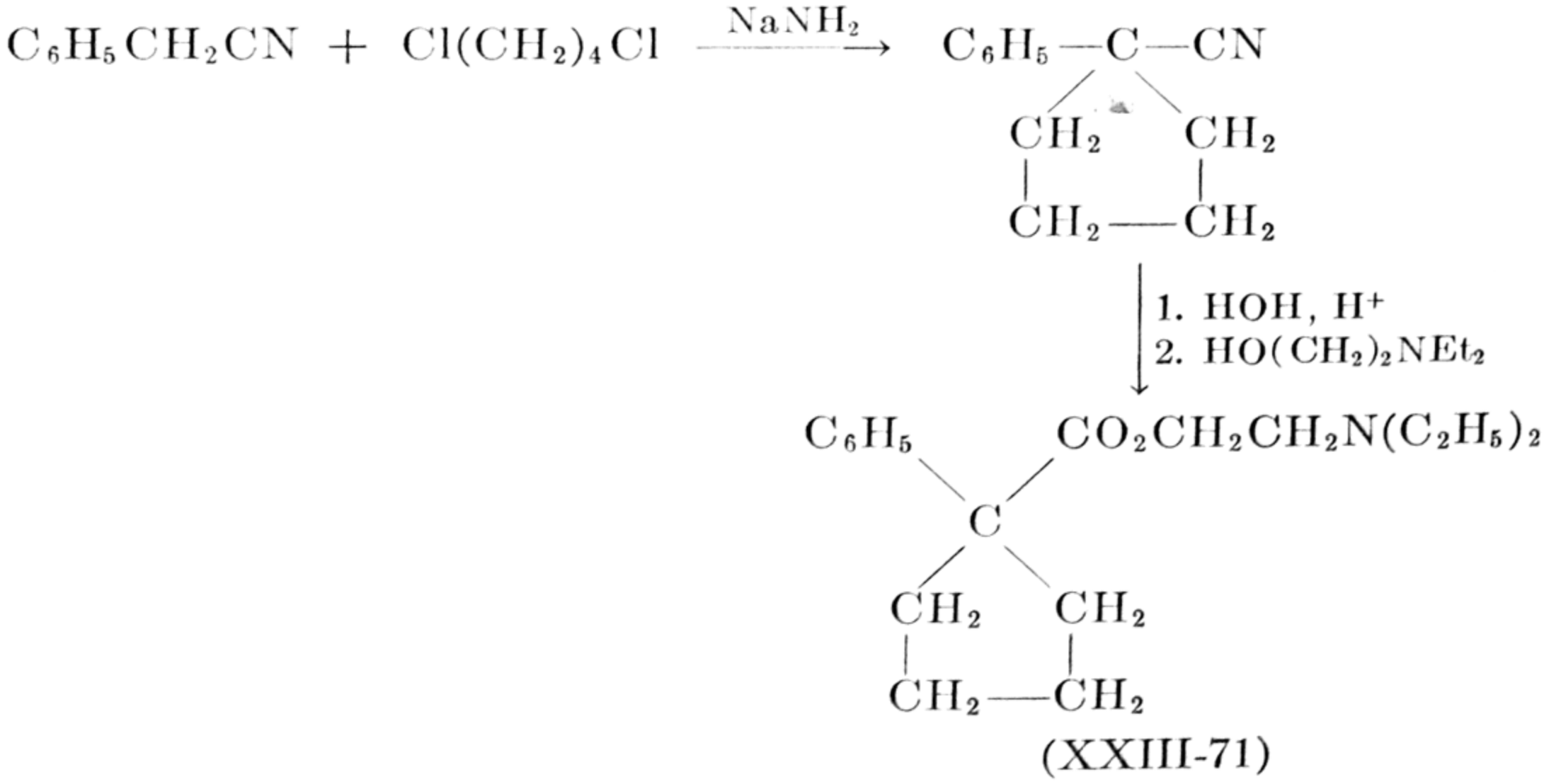


(XXIII-69)



(XXIII-70)

Many dialkylaminoalkyl esters of 1-phenylcycloalkanecarboxylic acids are pronounced antispasmodics.[52] The drug Panpartit, β-diethylaminoethyl 1-phenylcyclopentanecarboxylate (XXIII-71), is an example of this series. It has been synthesized by condensing benzyl cyanide with 1,4-dichlorobutane under the influence of sodamide. The nitrile group is then hydrolyzed, and the acid esterified with diethylaminoethanol.

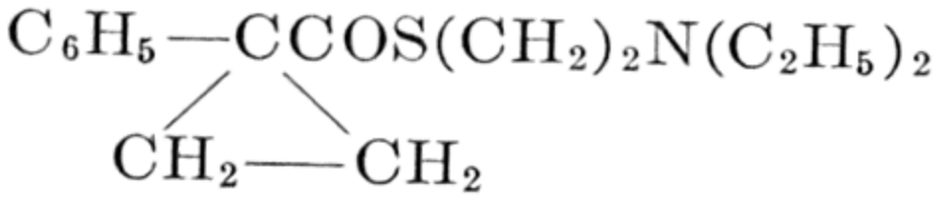


(XXIII-71)

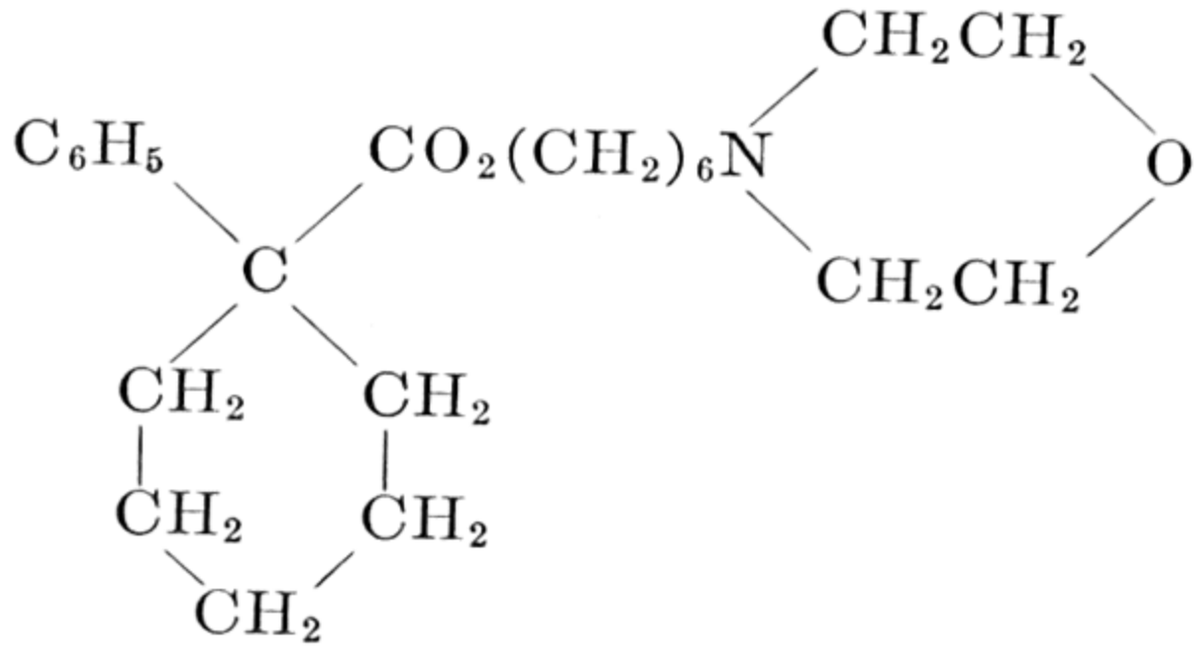
[48] Martin and Häfliger, U. S. Pat. 2,428,978 (1947).
[49] Wagner-Jauregg, Arnold, and Born, *Ber.*, **72,** 1551 (1939).
[50] Burger, Markees, Nes, and Yost, *J. Am. Chem. Soc.*, **71,** 3307 (1949).
[51] Chance, Dirnhuber, and Robinson, *Brit. J. Pharmacol.*, **1,** 153 (1946).
[52] Weston, *J. Am. Chem. Soc.*, **68,** 2345 (1946). Tilford, Van Campen, and Shelton, *J. Am. Chem. Soc.*, **69,** 2902 (1947).

Panpartit has been recommended for the control of spasms in Parkinsonism, but it also relieves bronchospasm in perfused guinea pig lungs made spastic by histamine or acetylcholine.

Other compounds in this series which deserve mentioning are 2-diethylaminoethyl 1-phenylcyclopropanecarbothiolate (XXIII-72), and 6-morpholinohexyl 1-phenylcyclohexanecarboxylate (XXIII-73). Both these derivatives are more active than papaverine and possess substantial neurotropic activity.



(XXIII-72)

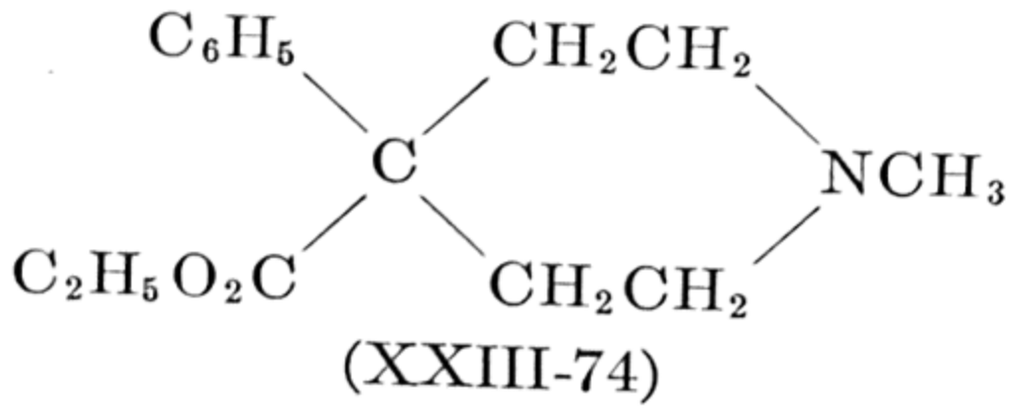


(XXIII-73)

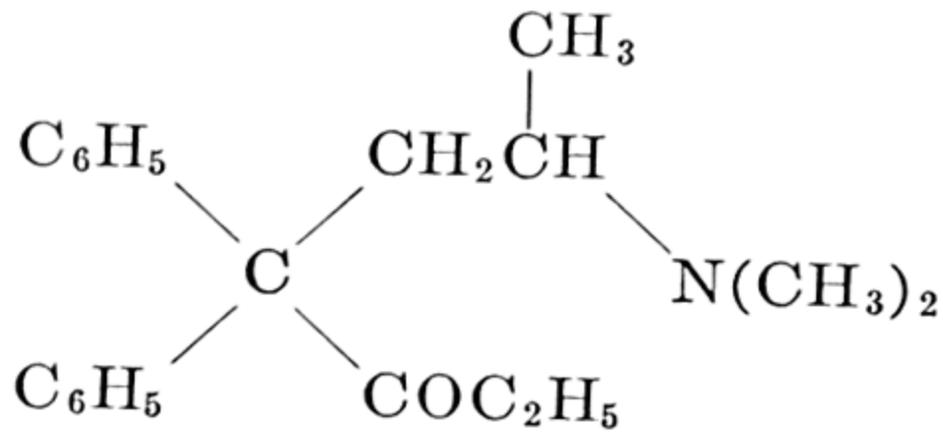
The presence of a phenyl group in these esters may not be of intrinsic importance since such a simple compound as β-diethylaminoethyl cyclopentane-carboxylate, cyclo-$C_5H_9CO_2(CH_2)_2NEt_2$, is capable of relaxing spastic muscles.[53]

VI. DEMEROL

There is little doubt that the drugs of the Demerol group were originally designed as antispasmodics, and that their powerful analgetic properties were discovered only during their pharmacological screening. Demerol (XXIII-74) itself may be conceived as an ester of phenylacetic acid in



(XXIII-74)



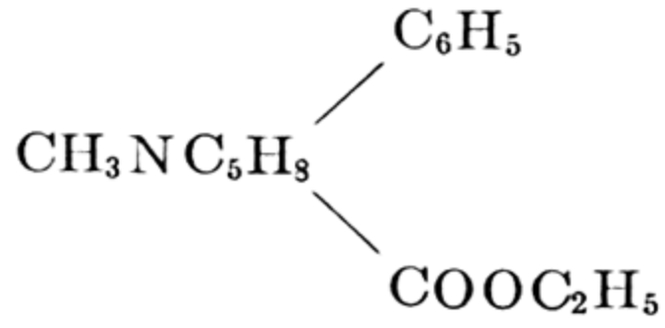
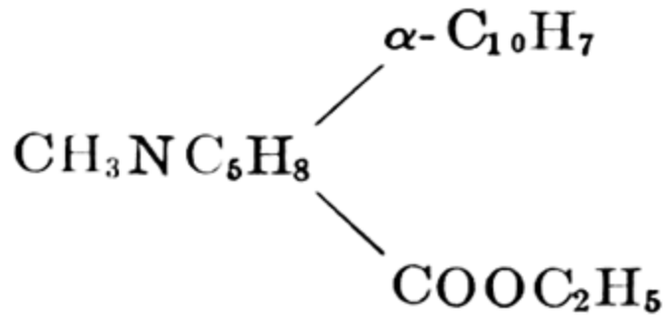
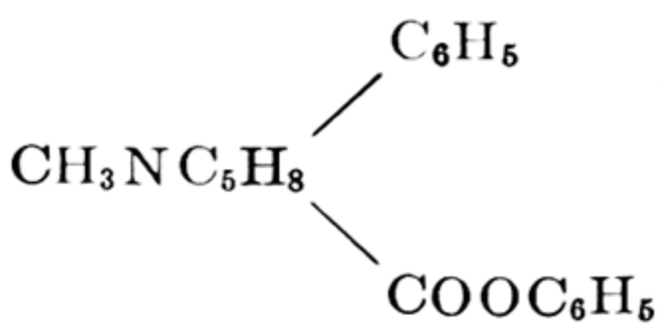
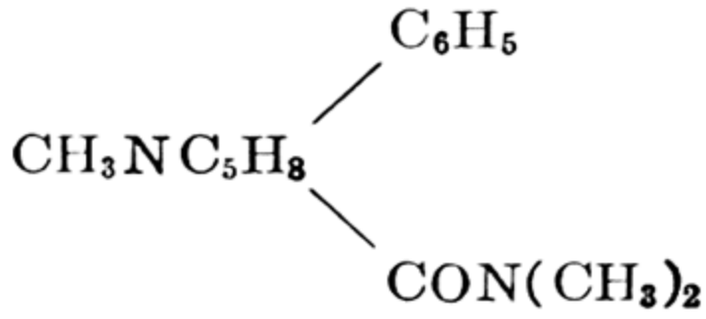
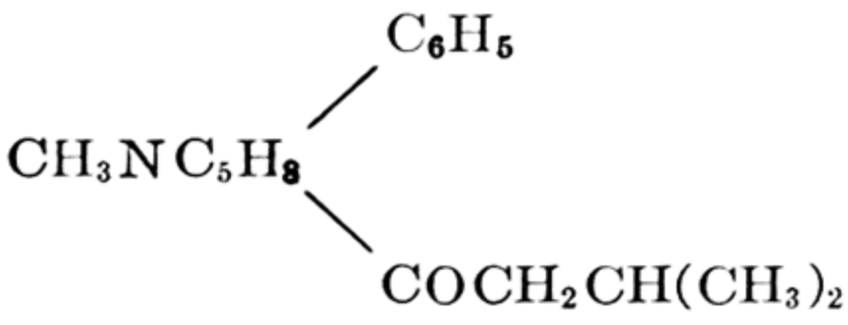
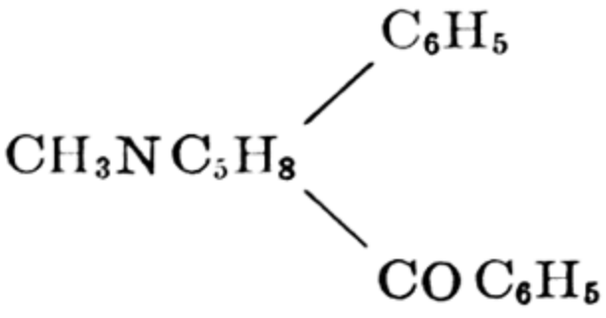
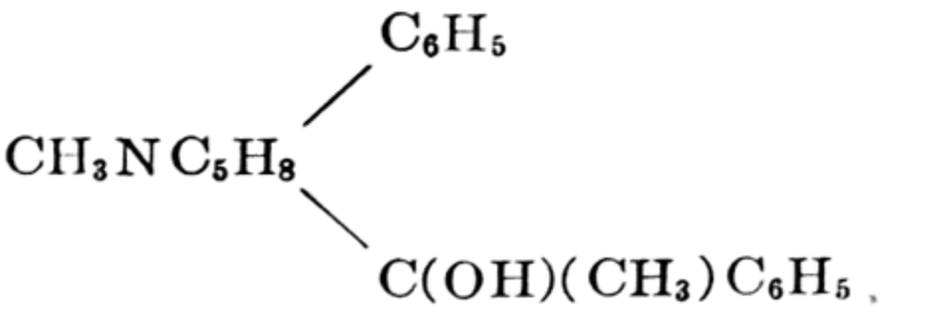
(XXIII-75)

which both α-hydrogens have been replaced by a piperidine ring. The basic function, customarily present in the ester group, has thus been moved into the body of the acyl portion.

[53] Suter, *Ind. Eng. News*, **27,** 19 (1949).

The chemistry and synthesis of Demerol has been discussed in the chapter on analgetics. The short Table V presents Demerol and a few of

TABLE V.[54] 4-PHENYL-N-METHYLPIPERIDINE DERIVATIVES

Compound		Carbamyl-choline	Ba	Hi
	(Demerol)	1	40	1000
		0.33	120	2000
		1	80	1000
		3	80	500
		3	60	1000
		10	200	4000
		10	80	2000

its analogs as antispasmodics. Carbamylcholine is used as a parasympathomimetic agent, and the blocking effect of the drugs is expressed in the same units as in Table III.

The other important group of analgetics containing a quaternary carbon atom and represented by methadon (Chapter XI) is even more closely related to the structure of diphenylacetic acid analogs. Methadon itself (XXIII-75) and many analogous drugs are effective myotropic antispasmodics.

The overlapping of antispasmodic (autonomic blocking) and analgetic properties in the Demerol and methadon group perhaps supports the newer views of relief from pain on the basis of an anticholinergic mechanism (Chapter XXI).

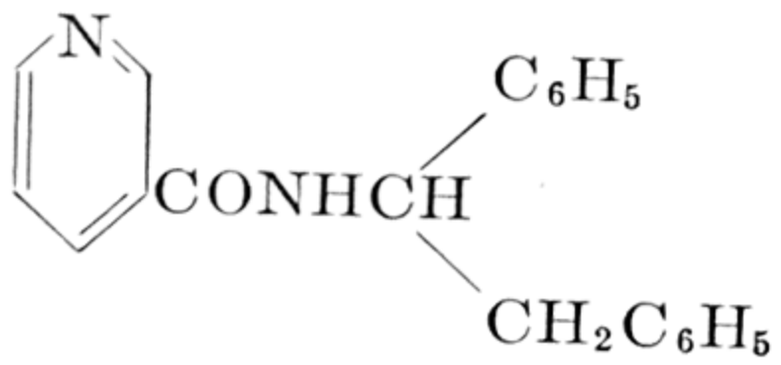
VII. SUBSTITUTED ACETAMIDE DERIVATIVES

Many α-di- and trisubstituted acetamide derivatives [$RR'R''CCONHCH_2CH_2N(C_2H_5)_2$] appear either slightly less or somewhat more active, and about as toxic as the corresponding acetate esters. Both types of antispasmodic activity show irregular fluctuations as small structural changes are applied.[55] From a series of primary trialkylacetamides, R_3CCONH_2, which were once or twice as active as papaverine, tributylacetamide, $(C_4H_9)_3CCONH_2$ was chosen as a drug and named Jecundal.[56]

Antispasmodic activity of various degrees was also observed among amides of α-aminoacids, for instance, $(C_6H_5)_2C(NH_2)CONH_2$.[57] Pronounced activity was observed for N-benzylnicotinamide (XXIII-76); a related amide, Lyspamin, nicotinamido-1,2-diphenylethane (XXIII-77), has been introduced as a powerful antispasmodic of long duration, especially for the preventive treatment of spastic conditions.[58]



(XXIII-76)



(XXIII-77)

[54] Adapted from Schaumann, *Arch. exptl. Path. Pharmakol.*, **196,** 109 (1940).
[55] Meier and Hoffman, *Helv. Med. Acta*, **7,** 106 (1941). Bockmühl and Erhart, German Pat. 731,560 (1943).
[56] Junkmann, *Arch. exptl. Pathol. Pharmakol.*, **195,** 175 (1940).
[57] Billman and Hidy, *J. Am. Chem. Soc.*, **65,** 760 (1943). Billman and Rendall, *J. Am. Chem. Soc.*, **66,** 540 (1944).
[58] Suter, Gordonoff, and Dubois, *Schweiz. med. Wochschr.*, **35,** 853 (1948).

VIII. CONCLUSIONS

Several investigators have tried to draw some conclusion about the cause of antispasmodic action from the large statistical material in this field of structurally allied compounds. These ideas have not been wholly successful, mainly because different pharmacodynamic mechanisms seem to be at work in the groups of neurotropic and myotropic drugs. Using nine diethylaminoethyl esters of diphenyl- and diphenylalkylacetic acids, Hirt[59] observed maximum antispasmodic potency in those derivatives which, in 1% solution, exhibited a surface tension of 40–45 d./cm. Several other related compounds, especially atropine and other esters containing alcoholic hydroxyl groups, did not fit into this scheme. The high activity of atropine and of esters of benzilic acids has been attributed to their ability to fasten themselves by three oxygen atoms (the ester group plus the alcoholic hydroxyl) to reactive positions at the surface of cell enzymes.[60] In this way, the approach of acetylcholine to the same positions is blocked. The greater molar potency of atropine as compared with Trasentine or Pavatrine may be accounted for by its "umbrella-like" shape which may mechanically or electrostatically inactivate adjacent cell receptors and render them unavailable for acetylcholine. In accord with this hypothesis it has been found that quaternization of the tertiary amino group in the esters of the Trasentine type often increases the antispasmodic activity of these drugs, perhaps by providing greater affinity to the centers occupied by acetylcholine.[61]

Quaternary atropinium salts have attained considerable curariform activity, and have been discussed in this connection in Chapter XXII.

It is difficult to draw the line between true antispasmodics and antihistaminic substances. Both prevent or relieve spasm caused by histamine, but in a different measure. The antihistaminic compounds exert this action at extremely low concentrations and in a highly specific manner while their effect on intestinal spasm is insignificant. The great interest in antihistaminics shown in recent years justifies their discussion in a special chapter.

[59] Hirt, *Helv. Chim. Acta*, **32,** 87 (1949).
[60] Pfeiffer, *Science*, **107,** 94 (1948).
[61] cf. Meier and Hoffman, *Helv. Med. Acta*, **7,** 106 (1941).

CHAPTER XXIV

Histamine and Antihistaminic Drugs

I. HISTAMINE, ANAPHYLAXIS AND ALLERGY

Histamine, β-(4-imidazolyl) ethylamine (XXIV-1) occurs in most body organs and fluids, and exerts a variety of pharmacodynamic actions, primarily on the blood vessels. One cannot classify histamine as a hormone although its manifestations would readily place it in this category. However, as far as it is known it is not secreted by an endocrine gland, and thus does not fall within the classical definition of hormones. More pertinent than the uncertainty of its origin is perhaps the fact that histamine is not concerned with the harmonizing effect of the endocrine hormones upon the



(XXIV-1)

whole body. It does not enter into the biological reactions catalyzed by other hormones but rather appears as the source of innumerable pathological conditions which can be traced to its liberation in the body fluids and its deposition in the tissues.

In carnivora, in monkeys and in man, small doses of injected histamine cause a fall in blood pressure by relaxation of the capillaries and smaller vessels although the larger arteries are constricted.[1] Vasodilation of the capillaries, and increase of arterial pressure lead to a loss of circulatory fluid into the surrounding tissues, a condition commonly identified with histamine shock. This is similar to traumatic shock, or to anaphylactic shock due to violent immunological reactions, and these observations have linked milder symptoms of anaphylaxis with manifestations of hypersensitivity in man.[2]

If a guinea pig is exposed to a sensitizing antigen as may be found in certain food stuffs, pollen, animal hair, etc., it begins to sneeze and rub its

[1] Barger and Dale, *J. Physiol.*, **40,** 38 (1910). Dale and Laidlaw, *J. Physiol.*, **41,** 318 (1910); **52,** 355 (1919).

[2] Mann, *Surg. Gynecol. Obst.*, **21,** 430 (1915). Cannon, *J. Am. Med. Assoc.*, **70,** 611 (1918). Best, Dale, Dudley, and Thorpe, *J. Physiol.*, **62,** 397 (1927).

nose in a manner similar to that of a man suffering from hay fever. If it receives too large a dose of the sensitizing compound, it will exhibit a severe and often lethal reaction called anaphylactic shock. This reaction resembles severe allergic reactions in humans. An animal can be made immune or refractory to shock by the injection of a small, usually non-toxic dose of the very agent or antigen which has produced its anaphylactic reaction. Likewise in man a similar immunity or refractory state can be produced by injecting small amounts of sensitizing materials. Desensitization to specific antigens can be carried out in a number of ways. For instance, a large number of small doses of extracts of pollen, animal dander, house dust, and fungi may be injected into the sensitized individual. However, this is a slow and tedious process which does not lead to a satisfactory disappearance of clinical symptoms within a short period of time. In more recent years, it has been found that both animals and men may become sensitized to virtually any chemical they may come in contact with. Drugs, dye stuffs, metallic salts, vaccines, antibiotics, eggs, vegetables and many other products may cause allergy.

While it was thought at first that only high molecular compounds such as polysaccharides and proteins can serve as antigens, Landsteiner and his students showed that simple chemicals when combined with larger molecules such as proteins or polysaccharides can be transformed into specific antigens. After the production of antigens has taken place, the organism of man or animal creates, in defense against the antigen, a specific antibody. The latter arises from the globulin fraction of the blood and is probably a steric replica in reverse of the antigen molecule. According to Pauling,[3] the antigen serves as a steric pattern upon which the polypeptide chain, ordinarily destined to become a globulin molecule, is built in a way deviating from its normal structure.

Antibodies alone are harmless, but when antibodies and allergens or anaphylactogens (antigens causing allergic or anaphylactic reactions) are brought together, a reaction sets in which is essentially a disturbance of the normal physico-chemical condition of the cell, and which results in the liberation of toxic substances.[4]

Histamine has been incriminated as the most readily recognizable component of this toxic mixture. It is found normally in small amounts in tissues, especially in the lungs, and is thus available for various reactions. It has been substantiated by many investigators that anaphylaxis as well as allergy in humans may be due at least in part, to a release of relatively large amounts of histamine. Attempts have been made to desensitize

[3] Pauling, *Endeavour*, **7**, 43 (1948).
[4] Boyd, *Fundamentals of Immunology*. Interscience, New York, 1945.

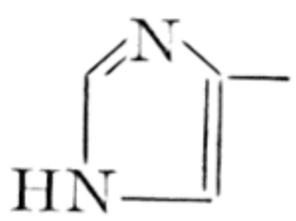
animals and man by small injections of histamine, but very little practical success has been achieved in this manner. Apparently, tolerance to histamine cannot be acquired in this way. Likewise, it has not been possible to desensitize animals by conjugates of histamine with diazotized proteins prepared according to the method of Landsteiner.

Certain arguments have been raised against the evidence that histamine is a proven factor in the production of anaphylactic symptoms. For instance, blood cannot be coagulated during anaphylactic shock, and histamine does not have any anticoagulant properties. But this particular phenomenon is probably due to a simultaneous release of the natural anticoagulant, heparin. It is also doubtful that *all* symptoms of allergy in men are caused by histamine. Nevertheless, it has been shown that certain skin reactions (wheal) of specific food allergies, and of urticaria behave as if they had been produced by direct administration of histamine.[5]

Histamine is probably formed from its precursor, the amino acid histidine, which in turn is liberated by proteolysis, or perhaps during an incomplete synthesis of proteins utilizing histidine. If we assume that histamine is the cause of numerous allergic and anaphylactic reactions, the interruption of the degradation of histidine to histamine would be a suitable point of interference with this chain of events. Unfortunately, the degradation of histidine by decarboxylation is complicated. Histidine (XXIV-2) is subject to the action of decarboxylases (with the probable aid of a coenzyme, pyridoxal pyrophosphate) as well as to that of amino acid oxidases. Any histamine (XXIV-1) formed in normal physiological quantities is apparently oxidized by the deaminase, histaminase or diamine-oxidase,[6] to imidazolyl aldehyde (XXIV-3) which is oxidized further by xanthine oxidase to imidazolylacetic acid (XXIV-4).

$$\underset{\text{(XXIV-2)}}{RCH_2CH(CO_2H)NH_2} \rightarrow \underset{\text{(XXIV-1)}}{RCH_2CH_2NH_2} \rightarrow \underset{\text{(XXIV-3)}}{RCH_2CHO} \rightarrow \underset{\text{(XXIV-4)}}{RCH_2CO_2H}$$

R =



It should thus be possible to block the catalytic activity of histidine decarboxylase but this has not proved feasible. Likewise, administration of histaminase *in vivo* has been unsuccessful although this enzyme destroys histamine readily *in vitro*. It is believed that histamine is ordinarily stored in an "inactive form" in the tissues and is released by different factors, for instance, the antibody-antigen reaction. There is no evidence that

[5] Lewis and Grant, *Heart*, **13,** 219 (1926).
[6] Best, *J. Physiol.*, **67,** 256 (1929).

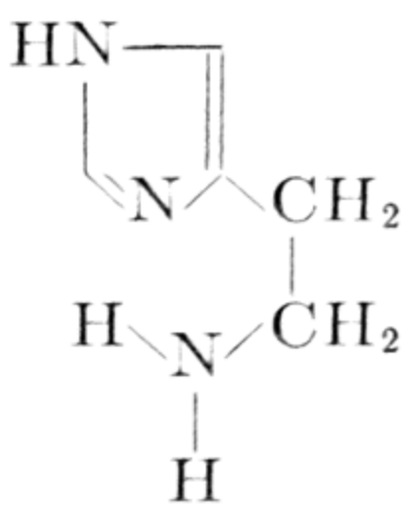
such excessive amounts of histamine which flood the organism suddenly can be disposed off by histaminase. This enzyme acts only slowly upon its substrate, and its *in vitro* behavior has added to the suspicion that our concept of deamination of even normal amounts of histamine may need to be revised. It is difficult to imagine that the slow-acting diamineoxidase should be responsible for the rapid disappearance of histamine from the blood and the tissues.

Liberation of histamine produces a number of symptoms in animals and men. Bronchial spasm in guinea pigs, intestinal and uterine spasm in guinea pigs and dogs, lowering of the blood pressure (hypotension) by capillary dilatation, increased capillary permeability, and the production of wheal and flare (skin reactions such as urticaria) are a few of them. Normal amounts of histamine also have the hormonal mission of stimulating secretory glands, especially the tear glands, nasal and pulmonary glands. The flow of gastric juice is stimulated, and injection of histamine may lead to hyperacidity within 20 to 30 minutes.

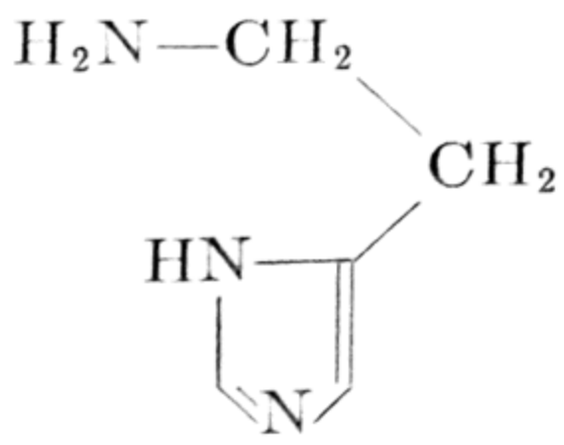
Dale[7] has indicated that histamine may be released by the so-called "antidromic" impulses at the endings of those terminal nerve branches which supply the network of minute blood vessels to the skin. Histamine has also been regarded as a mediator for cutaneous pain.[7a]

There exists the possibility that histamine does not act directly, but by intervention of released acetylcholine.[8] Some authors believe that histamine is bound in the tissues to protein in an inactive form, and that this protein plays the role of a fixed antibody. Introduction of an antigen causes combination of the antigen with the protein, and histamine is thereby released, as are also the similarly "inactive" acetylcholine and heparin.[9]

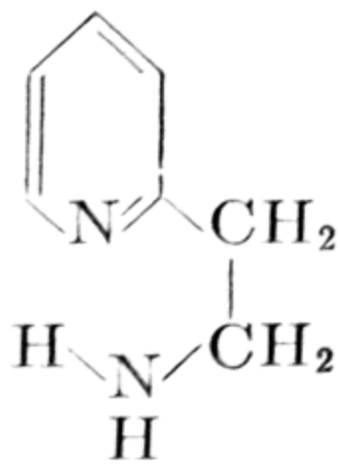
In an attempt to elucidate the decisive groups in the molecule of histamine, Nieman and Hays[10] synthesized 5-β-aminoethylimidazole



(XXIV-1)



(XXIV-5)



(XXIV-6)

[7] Dale, *Brit. Med. J.*, **2,** 889 (1948).

[7a] Rosenthal, *Proc. Soc. Exper. Biol. Med.*, **74,** 167 (1950).

[8] cf. Huttrer, *Experientia*, **5,** 53 (1949). Danielopolu, *Schweiz. med. Wochschr.*, **78,** 567 (1948).

[9] Parrot and Richet, *Compt. rend. soc. biol.*, **137,** 380 (1943).

[10] Nieman and Hays, *J. Am. Chem. Soc.*, **64,** 2288 (1942).

(XXIV-5), the isomer of histamine carrying the side-chain α to the secondary nitrogen atom of the ring. This compound has no longer histamine-like activity. Likewise, of the three isomeric 2-, 3-, and 4-(β-pyridyl)-ethylamines, only the 2-isomer (XXIV-6) lowers the blood pressure. This behavior may mean that the structural requirements for histamine-like activity should be the grouping $\overset{\text{(a)}}{\text{—CH—}}\overset{\text{(b)}}{\text{N—C—}}\text{CH}_2\text{CH}_2\text{NH}_2$ where

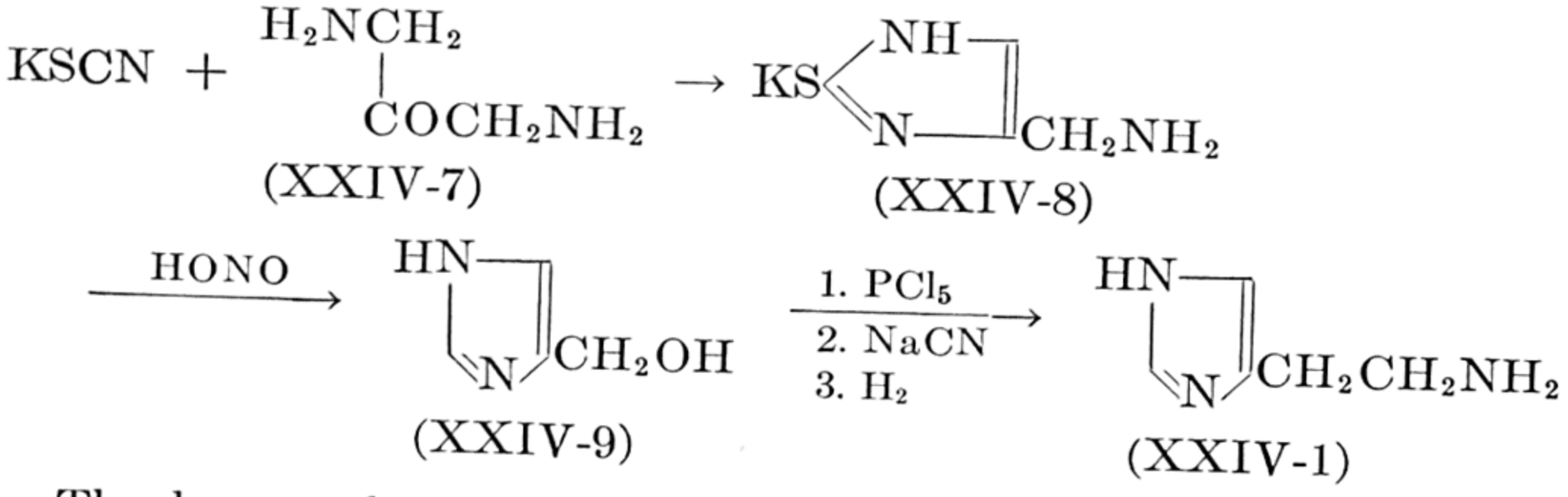
$$\text{CH}\ \text{(c)}$$

(a) = 1.36 ± 0.01 Å, (b) = 1.38 ± 0.02 Å, and (c) = 1.40 ± 0.01 Å. The nitrogen atoms of the cations of such compounds can be linked by hydrogen bonding.

A large number of other heterocyclic β-ethylamine derivatives has been studied in this connection[10a] but although some of them have as much as one-third the activity of histamine in its various pharmacodynamic manifestations, none of these compounds has rivaled histamine in all its biological aspects.

II. CHEMISTRY AND USES OF HISTAMINE

Histamine has been used to reduce hypertension in migraine headaches, and to prevent the Menière syndrome (vertigo, deafness and other vestibular disturbances) up to three months.[11] It also gives good results in Parkinsonism.[12] Histamine injections have been used in place of electroshock therapy in mental diseases. It may be that dilation of the blood vessels in the brain and the resulting increase of blood supply stimulate clearer thinking.



The drug can be prepared by decarboxylating histidine in high boiling inert solvents such as fluorene, or by bacterial enzymes. The latter method,

[10a] Lee and Jones, *J. Pharmacol. Exptl. Therap.*, **95,** 71 (1949).
[11] Horton, *Surg., Gynecol., and Obst.*, **72,** 417 (1947). Macy and Horton, *J. Am. Med. Assoc.*, **137,** 1110 (1948).
[12] Skinner, *Ohio State Med. J.*, **45,** 565 (1949).

followed by precipitation as the *o*-dichlorobenzenesulfonate, gives excellent yields.[13] Histamine can also be synthesized by condensing diaminoacetone (XXIV-7) with potassium thiocyanate, diazotizing the primary amino group of the resulting 4-aminomethyl-2-mercaptoimidazole (XXIV-8) with simultaneous removal of the thiol group, and conversion of 4-hydroxymethylimidazole (XXIV-9) to histamine by a nitrile synthesis.[14]

Structural modifications of histamine have been studied by many authors. The pharmacodynamic evaluation of compounds related to histamine has suffered from the necessity of defining which animal has been used, and which of the many diverse manifestations of histamine activity has been the object of the respective test. For example, N-methylhistamine ($C_3H_3N_2 \cdot CH_2CH_2NHCH_3$) is one-half as active as histamine in the cat, but exerts twice its action on the blood pressure of the guinea pig.

Modification of the ethylamine chain of histamine leads uniformly to inferior vasodilators. Shortening (—CH_2NH_2), lengthening (—$(CH_2)_{3-4}NH_2$) or branching (—$CH_2CH(CH_3)NH_2$) of the side chain always sharply reduces activity. Introduction of an alcoholic hydroxyl at the α-carbon (—$CHOHCH_2NH_2$) also decreases histamine effects. Methylation at N^1 or C^2 of the nucleus is equally detrimental. The disappearance of histamine activity in β-5-imidazolylethylamine (XXIV-5) has been mentioned above.

III. ANTIALLERGENIC DRUGS

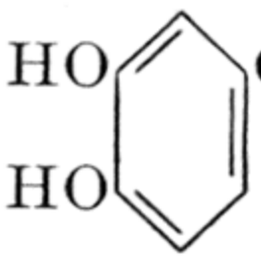
The treatment of allergies is complicated by the fact that a specific desensitizing agent has to be found for each specific antigen. It would be a distinct advantage if a method could be discovered which would desensitize an individual, or inhibit anaphylaxis in an animal by perhaps one and the same desensitizing agent. Support to this approach is given by the observation that although many different antigens have been found, the results of their action on the organism are virtually the same. They produce symptoms so closely related that it is impossible to say which allergen is responsible for them.

As in every type of research leading to new drugs, various chemicals have been tested in a random manner as a possible means of counteracting allergy or anaphylaxis. Among them were many chemicals which have since been recognized as potentiators of cholinesterase. Even fever therapies and infections with virulent organisms have been proposed, and reduction of barometric pressure, and other physical methods and agents have found temporary favor. Vitamins, particularly ascorbic acid and

[13] Galat and Friedman, *J. Am. Chem. Soc.*, **71,** 3976 (1949).
[14] Lévy-Brühl, Ungar, and Levillain, *Compt. rend.*, **204,** 1222 (1937).

vitamin D, hormones, for instance the sex hormones, and diethylstilbestrol derivatives have been used, the latter because so often great relief from allergy had been observed during pregnancy. It is known now that this phenomenon is due to increased secretion of antiallergenic adrenocortical hormones.

During these experiments it was discovered that certain compounds known to produce a rise in blood pressure could overcome rapidly the manifestations of allergy and anaphylaxis. Especially epinephrine (XXIV-10) and the alkaloid ephedrine (XXIV-11) have proved effective, and lately other synthetic drugs such as Propadrine, (XXIV-12), Paredrine



(XXIV-10): R = CH_3
(XXIV-14): R = $CH(CH_3)_2$



(XXIV-11): R = CH_3
(XXIV-12): R = H



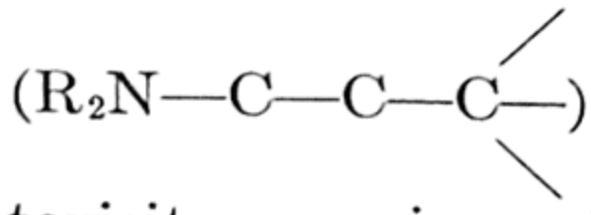
(XXIV-13)

(XXIV-13), and Aludrine (Isuprel, XXIV-14) have come into use for this purpose. They relieve allergic symptoms rapidly, and are used widely for the dissipation of catastrophic allergic conditions.

A number of other drugs show anti-allergic action, but apparently by a different mechanism. For instance, aminophylline (a molecular combination of aminopyrine and theophylline) seems to act by virtue of its ability to relax smooth muscles which are contracted in histamine-induced spasms. Iodides are useful because they stimulate the mucous glands of the bronchi to produce a thin non-obstructing secretion. Histidine exerts a weak antihistaminic action, but like that of other amino acids, its effect is uncertain.

IV. ANTIHISTAMINIC DRUGS

Virtually all the compounds grouped under this heading contain the structural unit $R_2N—C—C—X$ in which X is a group beginning with oxygen ($R_2N—C—C—O—$), nitrogen ($R_2N—C—C—N'—$) or carbon

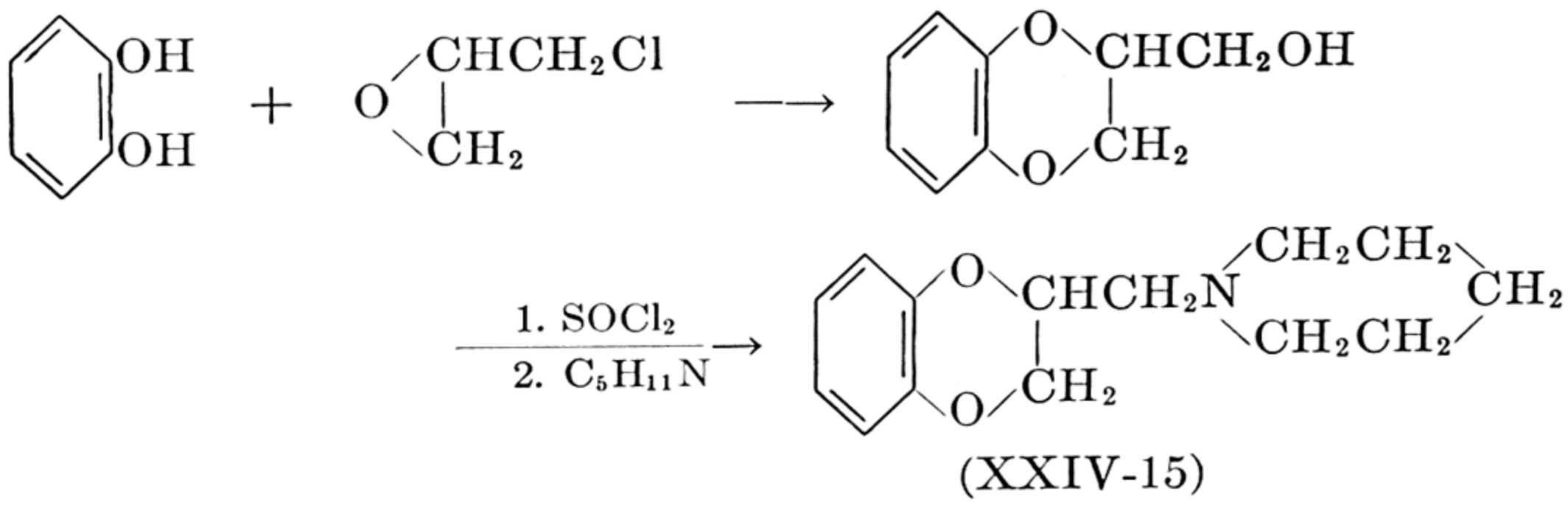


($R_2N—C—C—C—$). They counteract many manifestations of histamine toxicity, even in conditions (dermal allergies) in which the role of histamine is relatively insignificant. For this particular reason, many students of these compounds believe that the antihistaminic drugs do not act specifically

against histamine itself but that they are anti-allergic in general and modify factors, other than histamine, which participate in the allergic syndrome. Nevertheless, the restoration of normal health by these drugs in animals poisoned by many times the lethal dose of histamine is so spectacular that the name antihistaminic appears well-chosen.

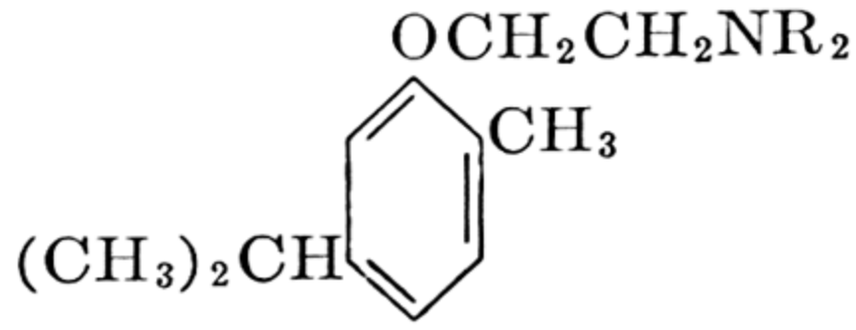
1. Early Benzodioxane Derivatives

While testing various compounds as potential antimalarials, Bovet and his associates[15] observed that 2-N-(piperidinomethyl)-1,4-benzodioxane (XXIV-15) could protect animals from bronchial spasm caused by aerosolized histamine. The compound had been synthesized from catechol and epichlorohydrin and subsequent treatment with piperidine, and was screened for alternative activities, among them antispasmodic properties.



(XXIV-15)

Since (XXIV-15) may be regarded as an ether, other aryl ethers containing basic side chains were tried. Of these, β-(5-isopropyl-2-methylphenoxyethyl) diethylamine (XXIV-16a) counteracted two to three lethal doses of histamine;[16] its dimethylamino homolog (XXIV-16b) was tolerated even better by humans.



(XXIV-16)
a: R = C_2H_5
b: R = CH_3

Isosteric replacement of the ether oxygen by amino nitrogen led Staub[17] into a series of aromatic derivatives of ethylenediamine of which N,N-di-

[15] Ungar, Parrot, and Bovet, *Compt. rend. soc. biol.*, **124,** 445 (1937).
[16] Bovet and Staub, *Compt. rend. soc. biol.*, **124,** 547 (1937). Fourneau and Bovet, *Arch. intern. Pharmacodynamie*, **46,** 178 (1933).
[17] Staub, *Ann. Inst. Pasteur*, **63,** 400, 420, 485 (1939).

ethyl-N′-phenyl-N′-ethylethylenediamine, $C_6H_5NCH_2CH_2N(C_2H_5)_2$, was

$$\begin{array}{c} | \\ C_2H_5 \end{array}$$

superior to the ethers mentioned above, since it counteracted two to six lethal doses of histamine. From his systematic studies, Staub concluded that the best hope for clinically useful antihistamine drugs lay in further variations of the structures $RR'NCH_2CH_2NR''_2$, or $ROCH_2CH_2NR''$, where R was phenyl or substituted phenyl, R′ alkyl or aralkyl, and R″ alkyl, best methyl. He thought that the ethers were more effective in relieving histamine-induced asthma, while the ethylenediamines were more specific in counteracting anaphylactic shock produced by administration of histamine.

The ethylenediamines fit into the working hypothesis that histaminase (diamineoxidase) might be able to attack them like histamine, and that their mode of action could be explained by a competition with histamine for available cell enzymes. This is supported by the fact that they obey the law of mass action in their relation to histamine over a wide range.

2. Pharmacological and Clinical Considerations

The method of testing against histamine activity has a profound bearing on the evaluation of these compounds. If, for instance, the antihistaminic activity of a compound is tested against one lethal dose of histamine (LD 100), all compounds show approximately the same activity. If, however, a standard dose of the antihistaminic is administered, and then the amount of histamine necessary to kill the protected animal is determined, wide variations are found for different drugs. Three milligrams/kg. of Benadryl protects a guinea pig against five lethal doses of histamine. Comparative figures for some other drugs are: Antergan, 6; Pyribenzamine, 37; and Neoantergan, 125.

The anti-allergic potency of a drug can be measured very accurately by a scratch test technique.[18] The drug is scratched in different dosages into sites on the body surface, and histamine is subsequently applied to the same scratches. By noting the point at which pretreated scratches fail to prevent skin-flare reactions of histamine, the minimum effective antihistaminic dose of the drug can be determined rapidly in one animal.

Clinically, the antihistaminic drugs have proved useful in the treatment of hayfever (vasomotor rhinitis), and skin reactions such as drug rashes, pruritis, contact dermatitis, urticaria and atopic dermatitis. Allergies causing the histamine flare reaction are benefited by these drugs. If treated early, attacks of common cold can be aborted. On the other hand, none of the present antihistaminics have proved very effective in acute

[18] Feinberg, *Quart. Bull. Northwestern Univ. Med. School*, **22,** 27 (1948).

asthmatic attacks, and they have not relieved histamine-induced gastric secretion. The pharmacological reason for this failure to act is still obscure. Surprisingly, epilepsy is influenced favorably by antihistaminic drugs.

Pellerat has made interesting observations on some apparent anomalies of the distribution of histamine between blood plasma and blood cells after administration of antihistaminic drugs. The reader is referred to a recent review on this subject.[19]

3. Basic Ethers

During the study of dialkylaminoalkyl aryl ethers prepared in Fourneau's laboratory at the Pasteur Institute, the following relations of structure and antihistaminic activity became apparent. Substitution of the benzene ring by alkyl groups of increasing size up to 4 carbon atoms raised activity but at the same time, antispasmodic activity decreased. If two different alkyl groups were present, their relative nuclear position in regard to the ether chain had no effect on activity. The best dialkylamino group was dimethylamine, followed by the diethylamino group which usually decreased activity and raised toxic side reactions. A piperidino group at the end of the ether chain was even less favorable.

a. Benadryl

(*1*) *Synthesis and Uses*

Independently of the French workers, antihistamine research got under way in the United States around 1943. The earliest experiments in the group of basic ethers were performed by Rieveschl who developed Benadryl as the first widely used antihistaminic substance.

Benadryl, β-dimethylaminoethyl-benzhydryl ether (XXIV-17), was patterned on the general molecular shape of the antispasmodic esters of diphenylacetic acid. The material was synthesized by condensing benzhydryl bromide (XXIV-18) prepared by actinic bromination of diphenylethane, with dimethylaminoethanol in the presence of potassium carbonate.[20]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{Light}]{Br_2} (C_6H_5)_2CHBr + HOCH_2CH_2N(CH_3)_2$$

(XXIV-18)

$$\xrightarrow[140°]{K_2CO_3} \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!\rangle CHOCH_2CH_2N(CH_3)_2$$

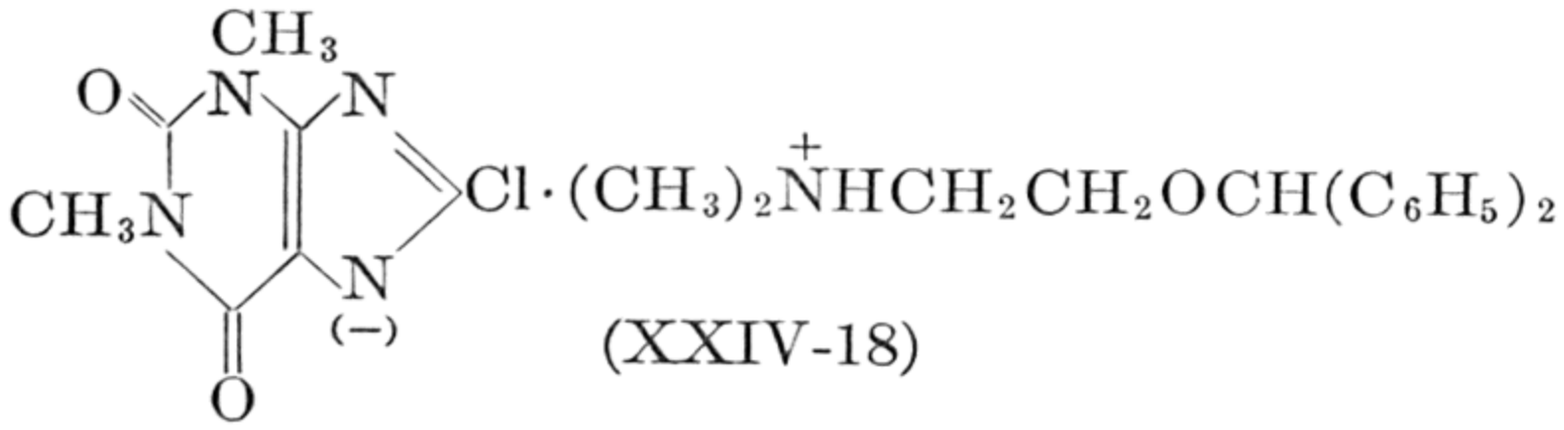
(XXIV-17)

[19] Huttrer, *Experientia*, **5**, 53 (1949).
[20] Rieveschl and Huber, U. S. Pat. 2,421,714 (1947).

Benadryl protects animals against bronchial asthma caused by histamine aerosol about 16 times more effectively than papaverine, and 33 times better than aminophylline. It has been used extensively in human hay fever and many other allergic conditions. Its main drawbacks are said to be side-effects such as drowsiness and nervousness in some individuals.[21]

Benadryl gives relief in Parkinson tremors, and antihistaminic drugs in general potentiate the sedative effects of barbiturates.[22] It is of interest that Benadryl antagonizes the depressor activity of acetylcholine.[23] On the other hand, it has no effect on antibody production, and on circulating antibodies which are supposed to be involved in the release of histamine.

The salt of Benadryl and 8-chlorotheophylline (XXIV-18, Dramamine) was developed by Cusic.[24] It has shown very great promise in preventing and relieving seasickness, nausea and vomiting during pregnancy, vertigo and radiation sickness. It is said to act directly on the vomiting center.[24]



(XXIV-18)

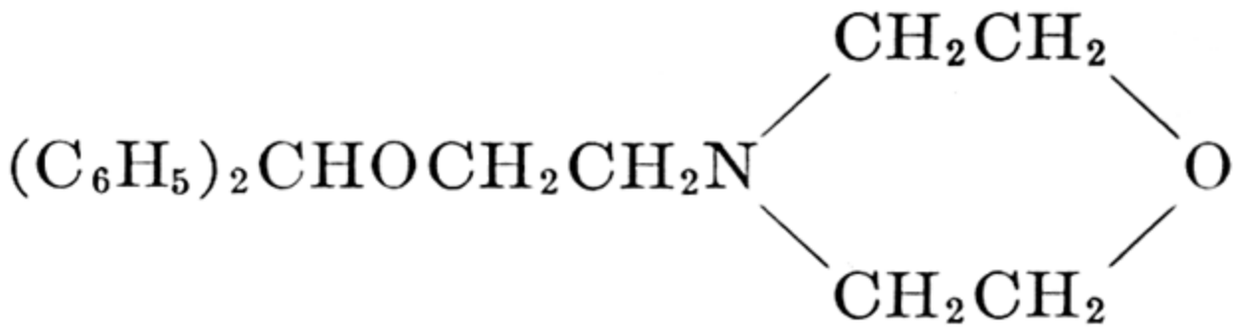
Scopolamine, Artane (XXIII-57), and Chlorocyclizine (XXIV-42) which, like Benadryl, exhibit an anticholinergic component, are also active in motion sickness.[24a]

(2) *Other Basic Ethers*

Chemical modifications of Benadryl have demonstrated that the morpholino analog (Linadryl, XXIV-19) is about half as active and as toxic as the dimethylamino compound. Substitution of the aromatic nuclei regularly decreases activity, while quaternization produces salts (XXIV-20) which are three times as spamolytic as Benadryl; they can be regarded as choline ethers and are noteworthy since they possess anticholinergic as well as antihistaminic properties.

A fairly active antihistaminic ether, 0.1 γ of which antagonized the effect of 1 γ of histamine on the isolated guinea pig gut was found in 2-benz-

[21] Loew, Kaiser, and Moore, *J. Pharmacol. Exptl. Therap.*, **83,** 120 (1945).
[22] Winter, *ibid.*, **94,** 7 (1948).
[23] Sherrod, Loew, and Schloemer, *J. Pharmacol. Exptl. Therap.*, **89,** 247 (1947). Dammin and Bukantz, *J. Am. Med. Assoc.*, **139,** 358 (1949).
[24] Gay and Carliner, *Bull. Johns Hopkins Hosp.*, **84,** 471 (1949). Carliner, Radman, and Gay, *Science*, **110,** 215 (1949). Beeler, Tillisch, and Popp, *Proc. Staff Meet. Mayo Clinic*, **24,** 477 (1949). Cusic, U. S. Pat. 2,499,058 (1950).
[24a] Chinn, Noell, and Smith, *Arch. Int. Med.*, **86,** 810 (1950).

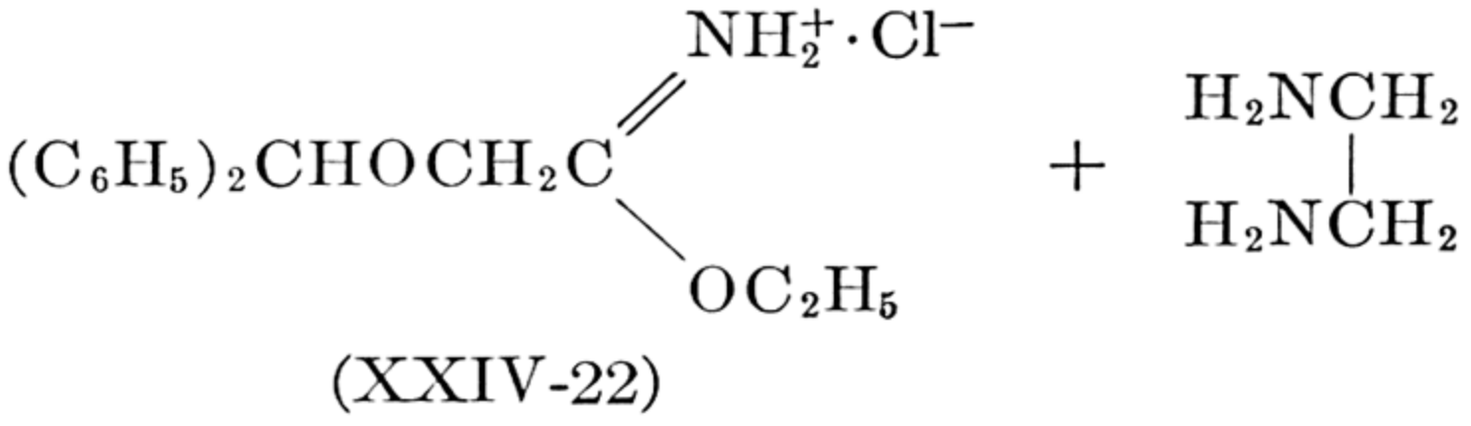


(XXIV-19)

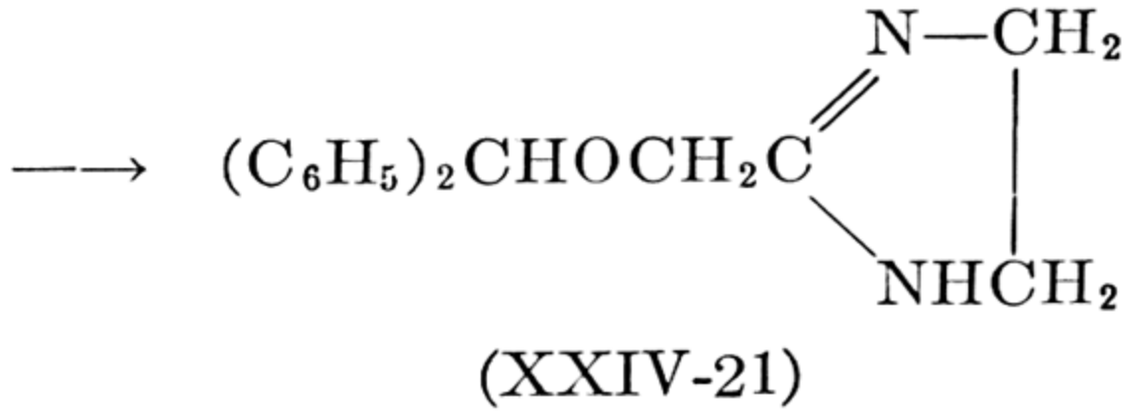
$$(C_6H_5)_2CHOCH_2CH_2N^+(CH_3)_3 \cdot I^-$$

(XXIV-20)

hydryloxymethylimidazoline (XXIV-21) which was synthesized from the imido ester (XXIV-22) and ethylenediamine.[25]



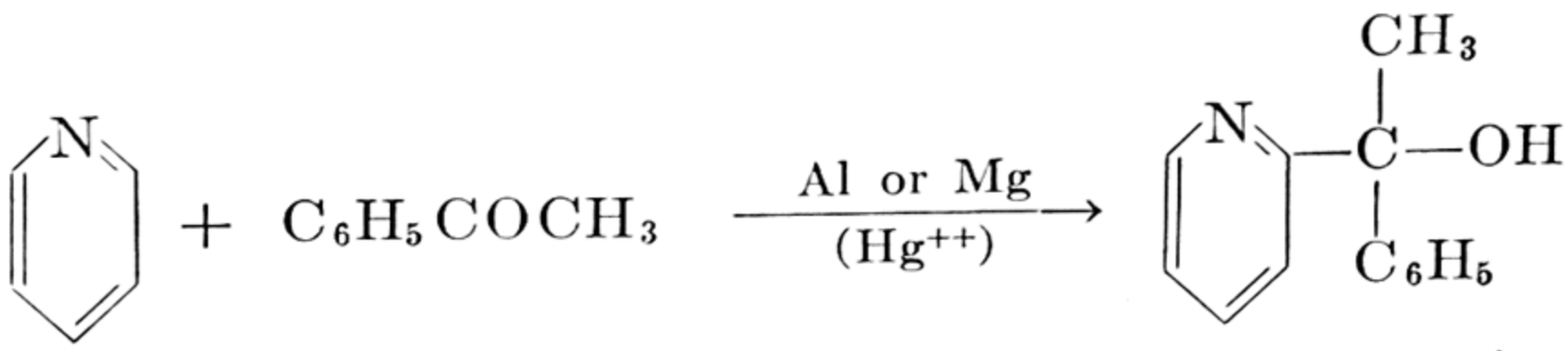
(XXIV-22)



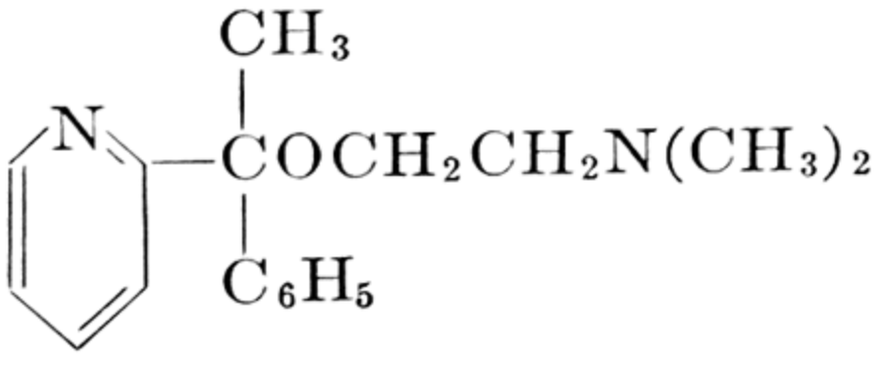
(XXIV-21)

Analogous compounds derived from phenol instead of from benzhydrol had a lower order of activity.

Decapryn (XXIV-23, α-(2-pyridyl)-α-phenylethyl-β'-dimethylaminoethyl ether) is a pyridine analog of Benadryl containing a quaternary carbon atom. It is synthesized by condensation of acetophenone with pyridine under the influence of aluminum or magnesium, and mercury.



(XXIV-24)

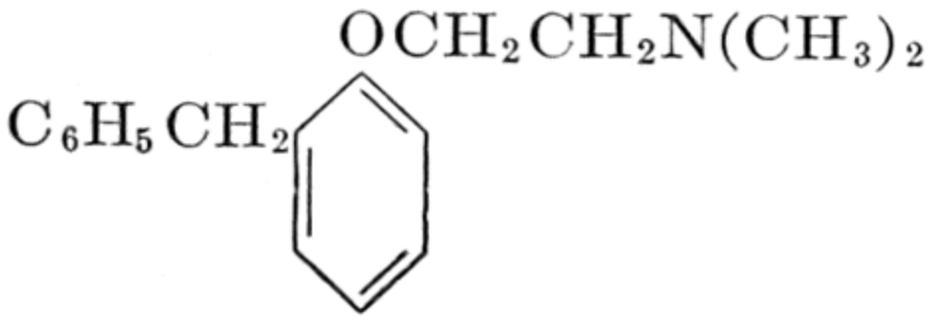


(XXIV-23)

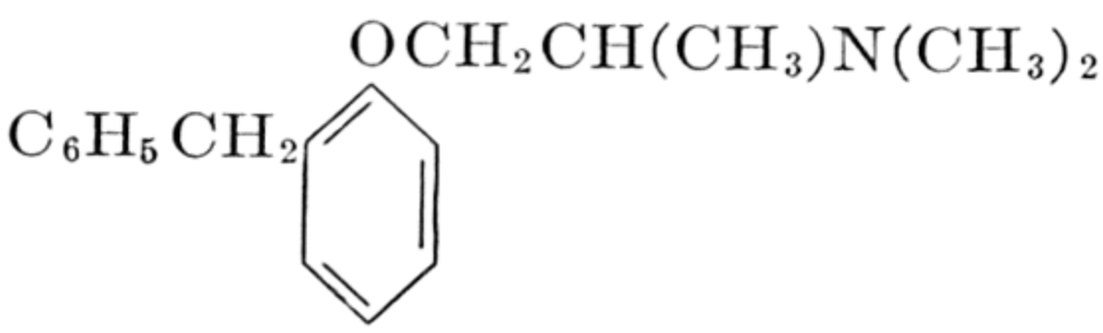
[25] Djerassi and Scholz, *J. Am. Chem. Soc.*, **69,** 1688 (1947).

The sodium derivative of the intermediary tertiary alcohol (XXIV-24) is then converted to the drug by reaction with dimethylaminoethyl chloride.

The most active antihistaminic agents in the series of basically substituted ethers are derived from *o*-benzylphenol. For example, *o*-benzylphenyl β-dimethylaminoethyl ether (XXIV-25), as well as its 4-chloro and 5-methyl derivatives show increased potency. The most effective compound in this group (4.6 times Benadryl) contains a branched aliphatic side chain (XXIV-26).



(XXIV-25)

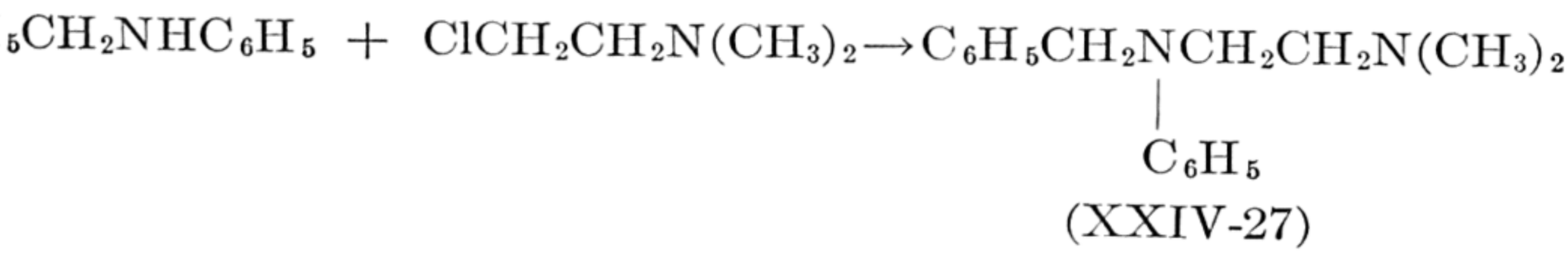


(XXIV-26)

4. Derivatives of Ethylenediamine

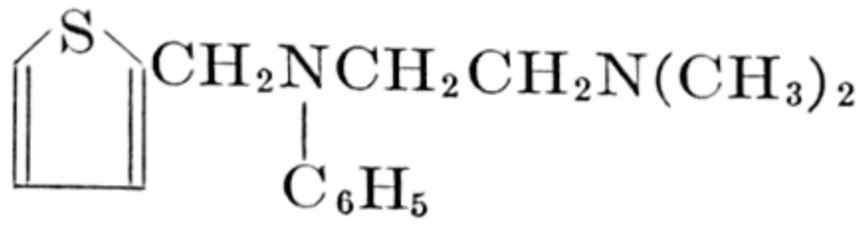
a. Antergan

In an extension of their early studies of compounds of the type $ArN(R)CH_2CH_2NR'_2$, Staub and Bovet[26] observed that highest antihistaminic activity could be attained if R was benzyl or an analogous group containing a heterocyclic nucleus, and R′ was methyl. The first useful drug in this series was Antergan[27] (XXIV-27) which was prepared from N-benzylaniline and dimethylaminoethyl chloride in the presence of potassium carbonate.

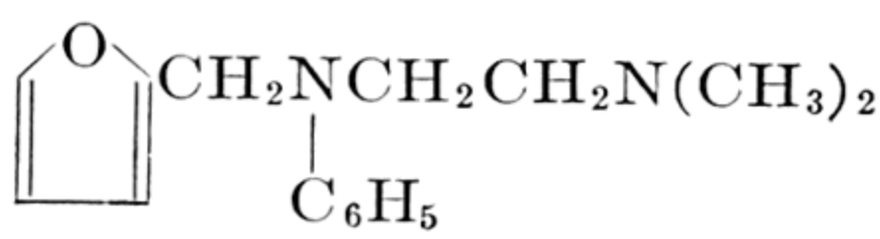


(XXIV-27)

Replacement of the benzyl group in Antergan by 2-thenyl produces the drug Diatrin (XXIV-28) which is said to be less sedative than the phenyl analog. The 2-methylfuryl isostere (XXIV-29) has been reported to have similar activity.



(XXIV-28)



(XXIV-29)

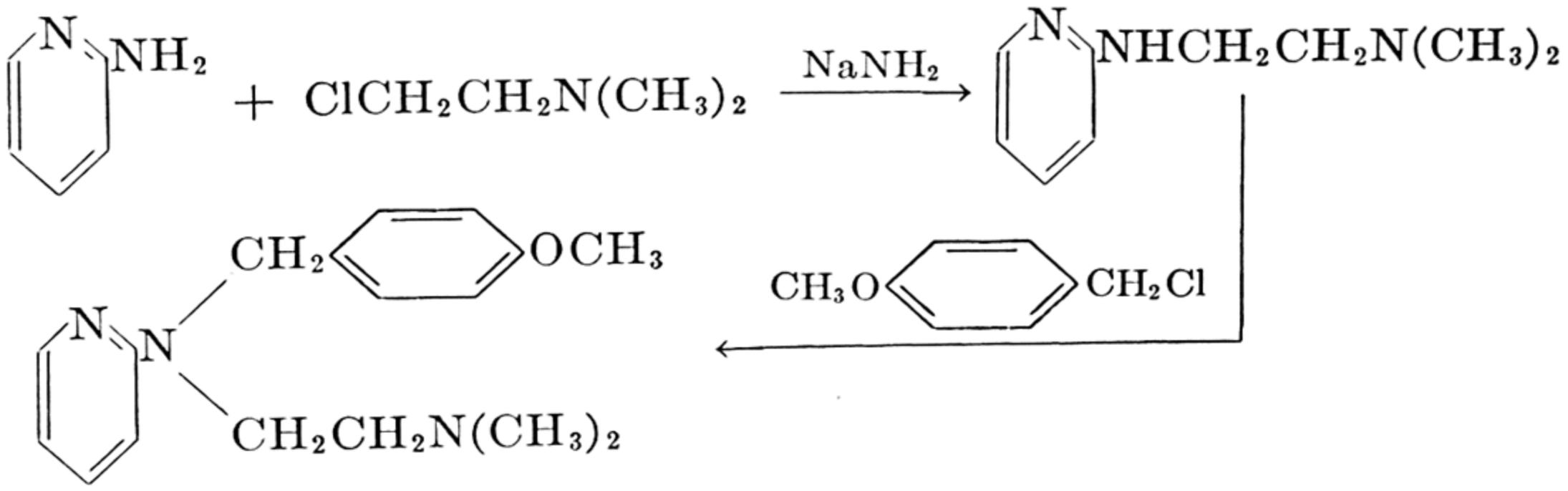
[26] Staub and Bovet, *Compt. rend. Soc. biol.*, **125,** 818 (1937).

[27] Halpern, *Arch. internat. Pharmacodynamie*, **68,** 339 (1942). Mosnier, French Pat. 913,161 (1943).

b. Neoantergan

If the phenyl group of Antergan is replaced by 2-pyridyl, and the benzyl group by *p*-methoxybenzyl, Neoantergan (XXIV-30) is obtained. This drug counteracts thirty to sixty times its weight of histamine[28] and is about three times more effective than Antergan. Neoantergan initiated the series of heterocyclic antihistaminic derivatives of ethylenediamine which has furnished some of the most effective and least toxic drugs in this group.

The syntheses of Neoantergan are typical of the preparative approaches of many similar compounds. They have been described in the first paper published on this subject in the United States.[29] The preferred and most economical method for Neoantergan is the condensation of α-aminopyridine with dimethylaminoethyl chloride in the presence of sodamide or lithamide, followed by treatment with *p*-methoxybenzyl chloride.



(XXIV-30)

Neoantergan is preferred by many physicians because it elicits a minimum of drowsiness. A clinical comparison of twelve antihistaminic drugs has recently been published.[30]

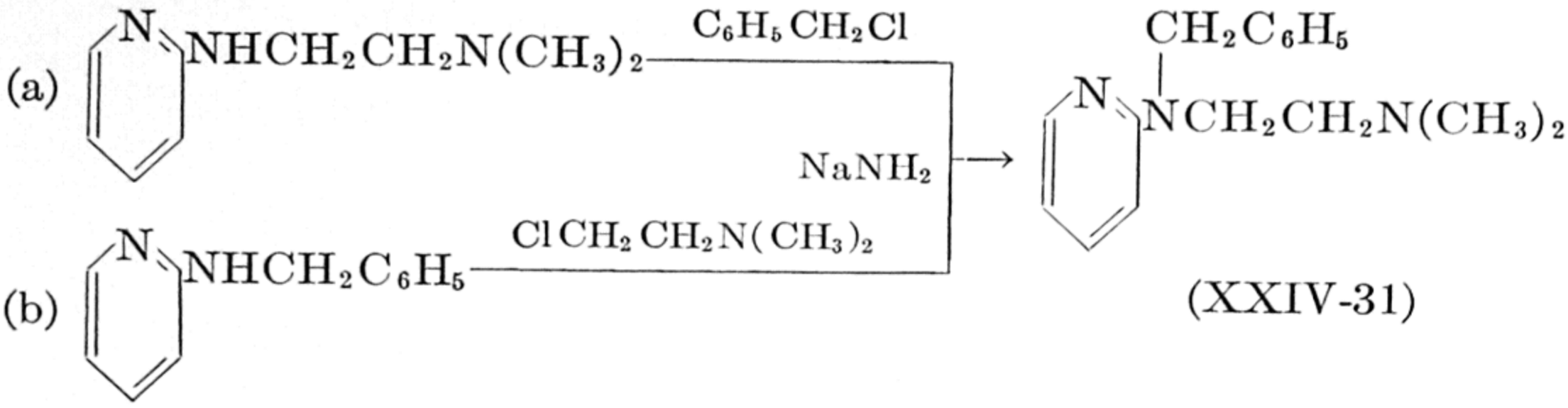
c. Pyribenzamine

The earliest substituted diamine developed in American laboratories was Pyribenzamine (XXIV-31).[29] It may be prepared (a) by condensing N,N-dimethylaminoethyl-α-aminopyridine with benzyl chloride, or (b) by treating 2-benzylaminopyridine with dimethylaminoethyl chloride; both reactions proceed in the presence of sodamide.

[28] Halpern and Walthert, *Compt. rend. soc. biol.*, **139,** 402 (1945). Bovet, Horclois, Horclois, and Walthert, *ibid.*, **138,** 99 (1944); Horclois, U.S. Patent, 2,502,151 (1950).

[29] Huttrer, Djerassi, Beears, Mayer, and Scholz, *J. Am. Chem. Soc.*, **68,** 1999 (1946).

[30] Schwartz and Wolf, *J. Allergy*, **20,** 32 (1949). Sternberg, Perry, and LeVan, *J. Am. Med. Assoc.*, **142,** 969 (1950).



(XXIV-31)

The drug's structure closely resembles that of Neoantergan, the latter being the *p*-methoxy derivative. Although Neoantergan has been judged superior[31] to most current antihistaminic drugs including Pyribenzamine in animals, the latter has remained one of the most widely prescribed drugs in hay fever and other allergies.

So many compounds having structures analogous to Pyribenzamine and Neoantergan have been made available to the physician that the choice of a suitable agent has become one of personal preference. The differences in side-effects are not appreciable but the individual drugs possess properties which make them particularly suited for the treatment of special allergy manifestations. Only a few of these compounds will be discussed here; the most popular drugs and their formulas are listed in Table I.

d. Neohetramine

Hetramine and Neohetramine are pyrimidine derivatives, Hetramine corresponding to its pyridine analog, Pyribenzamine, while Neohetramine may be compared structurally to Neoantergan. Neohetramine is said to have an activity almost comparable to that of Pyribenzamine but its toxicity is lower.[32] Like other antihistaminics, Neohetramine has been recommended for use with streptomycin in exudative human tuberculosis to reduce the allergic reaction of the host to the antibiotic, and to the hypersensitizing spread of the tubercle bacillus in the body.[33] Neohetramine has also become the active component of a popular "cold-aborting" drug, Anahist.

e. Thiophene Derivatives

The 2-thenyl isostere of Pyribenzamine, (Thenylene, Histadyl, Thenfadil) is closely related to Pyribenzamine in toxicity and dosage level.[34]

[31] Winter, *Federation Proc.*, **6,** 228 (1947).

[32] Friedman and Tolstooushov, U. S. Pat. 2,465,865 (1949).

[33] Duca and Scudi, *Ann. Allergy*, **7,** 318 (1949). Judd and Henderson, *ibid.*, **7,** 306 (1949).

[34] Feinberg and Bernstein, *J. Lab. Clin. Med.*, **32,** 1370 (1949). Weston, *J. Am. Chem. Soc.*, **69,** 980 (1947). Kyrides, Meyer, and Zienty, *J. Am. Chem. Soc.*, **69,** 2239 (1947).

TABLE I. SOME ANTIHISTAMINIC SUBSTANCES

Brand Name (and/or generic Name)	Chemical Name	Formula
Benadryl (Diphenhydramin) (Amidryl)	β-Dimethylaminoethyl benzhydryl ether	$(C_6H_5)_2CHOCH_2CH_2N(CH_3)_2$
Linadryl	β-Morpholinoethyl benzhydryl ether	$(C_6H_5)_2CHOCH_2CH_2N$ with CH_2CH_2 / CH_2CH_2 / O
Decapryn (Doxylamine)	(β-Dimethylaminoethoxy)-methyl-phenyl-(2-pyridyl) methane	$C_6H_5—C(CH_3)(OCH_2CH_2N(CH_3)_2)$ with 2-pyridyl
	o-Benzylphenyl-(β-dimethylaminoethyl)-ether	$C_6H_5CH_2$ / $OCH_2CH_2N(CH_3)_2$
2325 R(hone) P(oulenc)	N,N-Dimethyl-N′-phenyl-N′-ethylethylenediamine	$C_6H_5NCH_2CH_2N(CH_3)_2$ / C_2H_5
Antergan (Lergitin, Bridal)	N,N-Dimethyl-N′-phenyl-N′-benzylethylenediamine	$C_6H_5CH_2NCH_2CH_2N(CH_3)_2$ / C_6H_5
Pyribenzamine (Tripelennamine)	N,N-Dimethyl-N′-(2-pyridyl)-N′-benzylethylenediamine	$C_6H_5CH_2NCH_2CH_2N(CH_3)_2$ with 2-pyridyl
Diatrin	N,N-Dimethyl-N′-phenyl-N′-2-thenylethylenediamine	$C_6H_5NCH_2CH_2N(CH_3)_2$ / CH_2 / 2-thienyl

TABLE I (*Continued*)

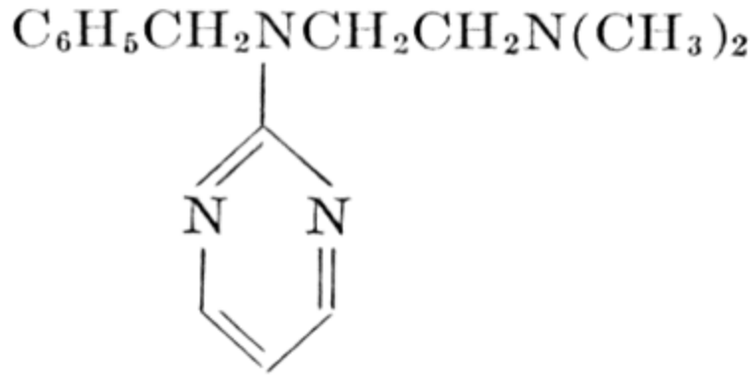
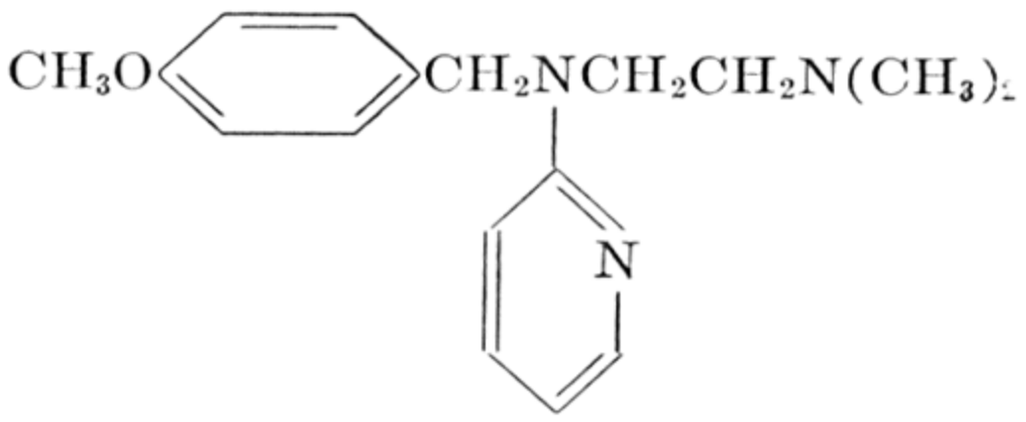
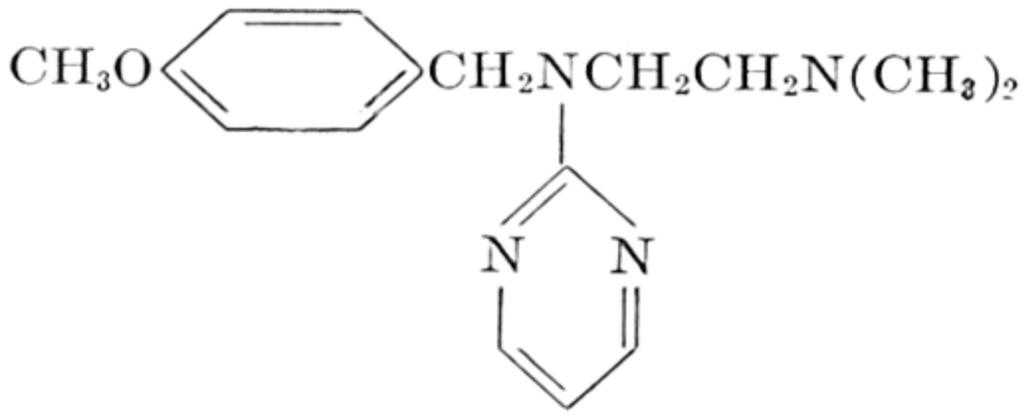
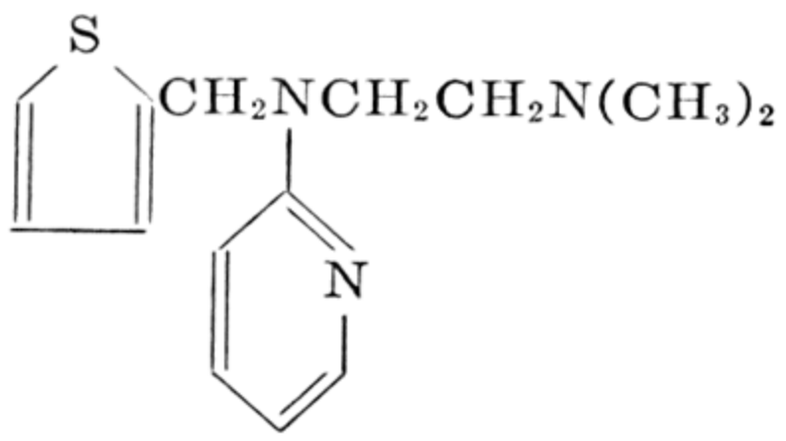
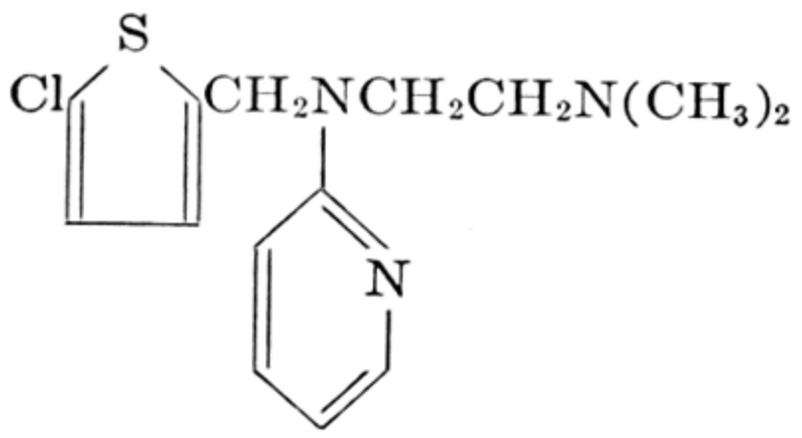
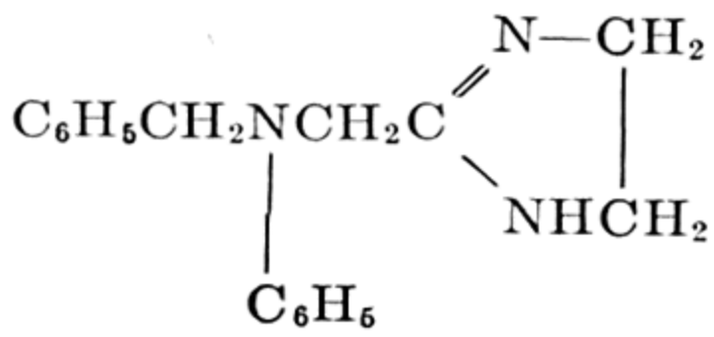
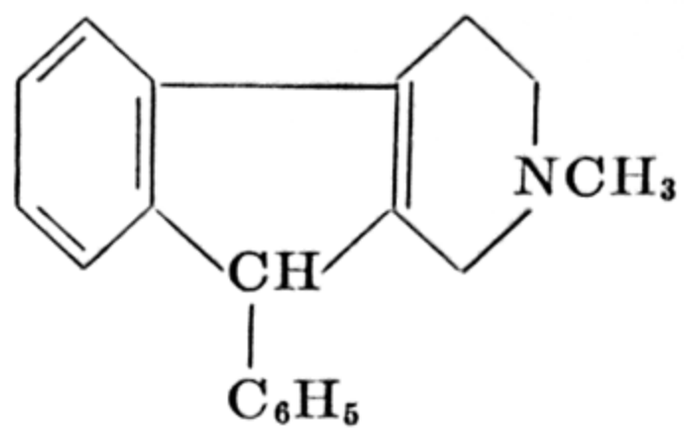
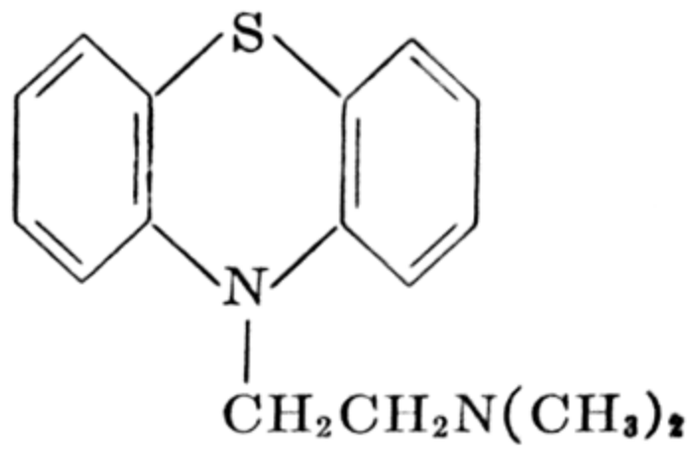
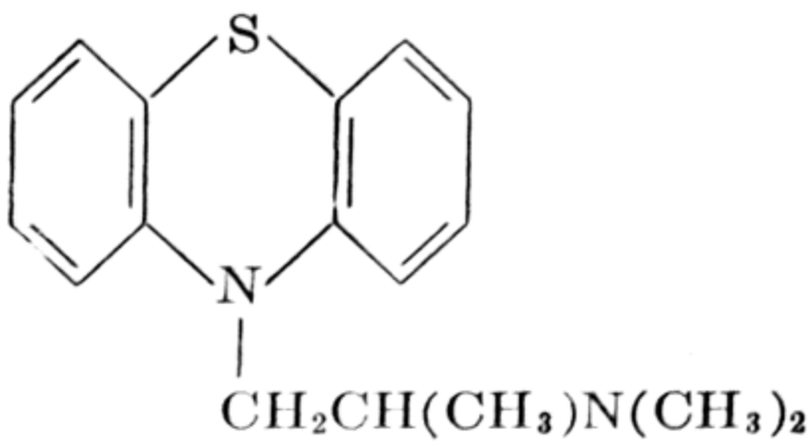
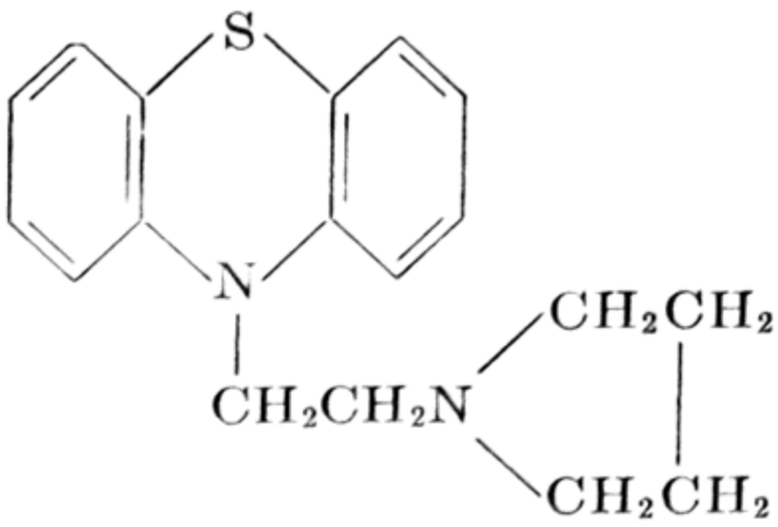
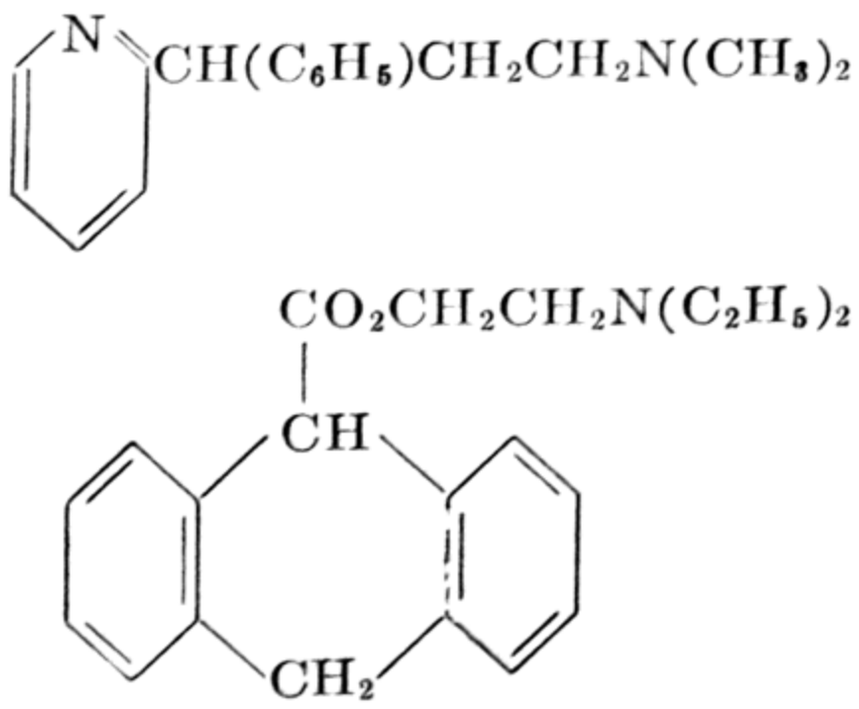
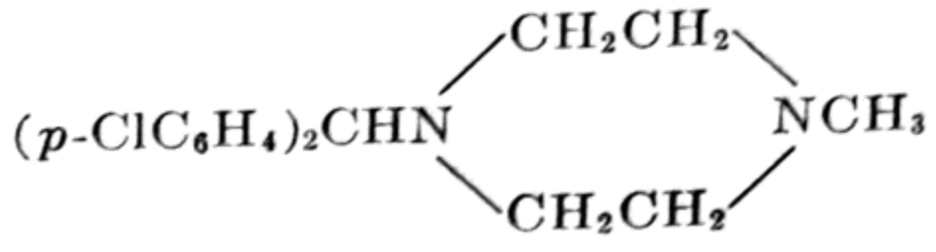
Brand Name (and/or generic Name)	Chemical Name	Formula
Hetramine	N,N-Dimethyl-N′-(2-pyrimidyl)-N′-benzylethylene-diamine	
Neoantergan (Anthisan, Pyranisamine)	N,N-Dimethyl-N′-(4-methoxybenzyl)-N′-(2-pyridyl) ethylenediamine	
Neohetramine	N,N-Dimethyl-N′-(4-methoxybenzyl)-N′-(2-pyrimidyl) ethylenediamine	
Thenylene (Histadyl, Metapyrilene, Thenylpyramine, Thenfadil)	N,N-Dimethyl-N′-(2-thenyl)-N′-(2-pyridyl) ethylenediamine	
Chlorothen	N,N-Dimethyl-N′-(5-chloro-2-thenyl)-N′-(2-pyridyl) ethylenediamine	
Antistin	2-(N-Phenyl-N-benzylaminomethyl) imidazoline	

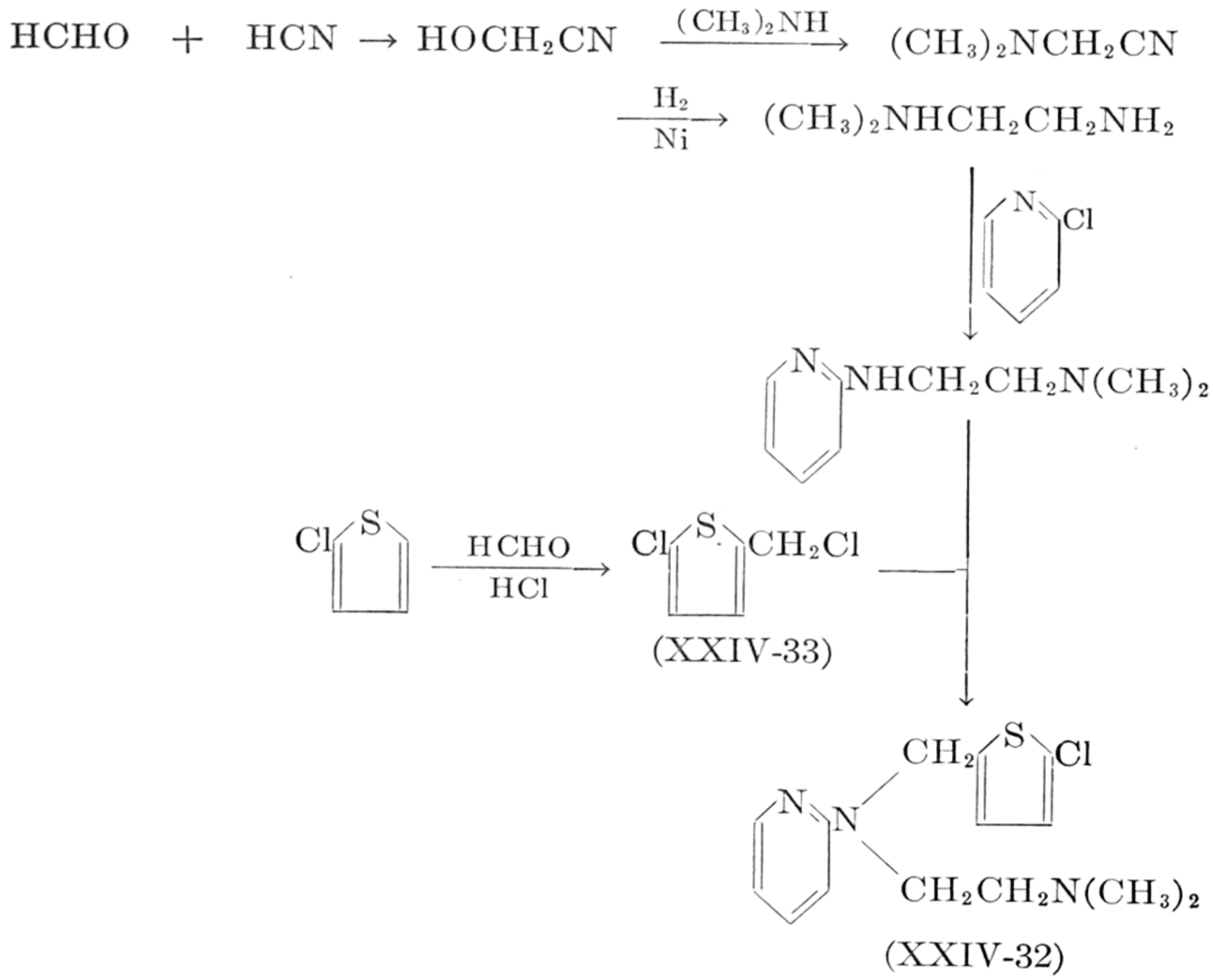
Table continued

TABLE I (*Continued*)

Brand Name (and/or generic Name)	Chemical Name	Formula
Thephorin (Phenindamine) (XXIV-48)	2-Methyl-9-phenyl-1,2,3,4-tetrahydro-pyridindene	
RP-3015 (Diparcol)	10-β-Dimethylaminoethylphenothiazine	
RP-3277 (Phenergan)	10-(2-Dimethylamino-1-propyl)-phenothiazine	
Pyrrolazote	10-(β-Pyrrolidinoethyl) phenothiazine	
Trimeton	1-(N,N-Dimethylamino)-3-phenyl-3-(α-pyridyl) propane	
Hydrillin	Diethylaminoethyl 9,10-dihydroanthracene-9-carboxylate	
Di-Paralene (Perazil, Chlorcyclizine)	1-(p-Chlorobenzhydryl)-4-methylpiperazine	

Several compounds resembling Thenylene, but containing halogenated thiophene nuclei, show increased antihistamine activity and lowered toxicity. The 5-chloro derivative (Chlorothen) is reported to be twice as active and one-half as toxic as Pyribenzamine, and to have twice its duration of action. Thenylene also leads to prompt subsidence of manic symptoms not responding to sedatives.[34a]

The synthesis of Chlorothen (XXIV-32) consists of a condensation of α-chloropyridine with β-dimethylaminoethylamine followed by treatment with 5-chloro-2-thenyl chloride. (XXIV-33). The latter is prepared by chloromethylation of 2-chlorothiophene.[35]

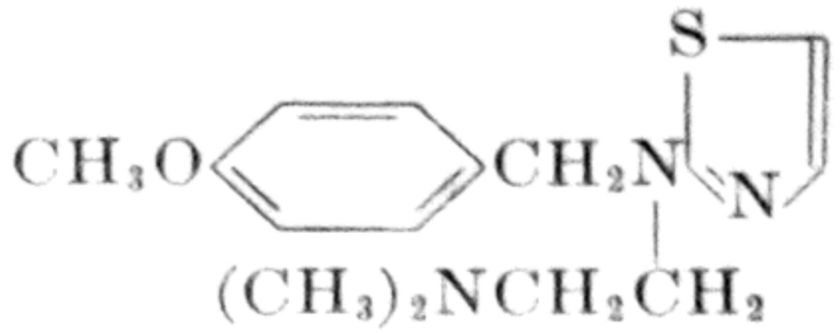


(XXIV-32)

The non-chlorinated 3-thenyl analog has about 1.5 times the activity of Thenylene. The 2-methylfuryl group may also replace the benzyl group of Pyribenzamine without significant change in antihistaminic potency.

The thiazole isostere of Neoantergan, N,N-dimethyl-N′-2-thiazolyl-N′-*p*-methoxybenzyl ethylenediamine (XXIV-34), has a low incidence of side reactions.[36]

[34a] Bryant, *Am. Practitioner*, **1**, 132 (1950).
[35] Clapp, Clark, Vaughn, English, and Anderson, *J. Am. Chem. Soc.*, **69**, 1549 (1947).
[36] Bernstein and Feinberg, *J. Lab. Clin. Med.*, **34**, 1007 (1949).

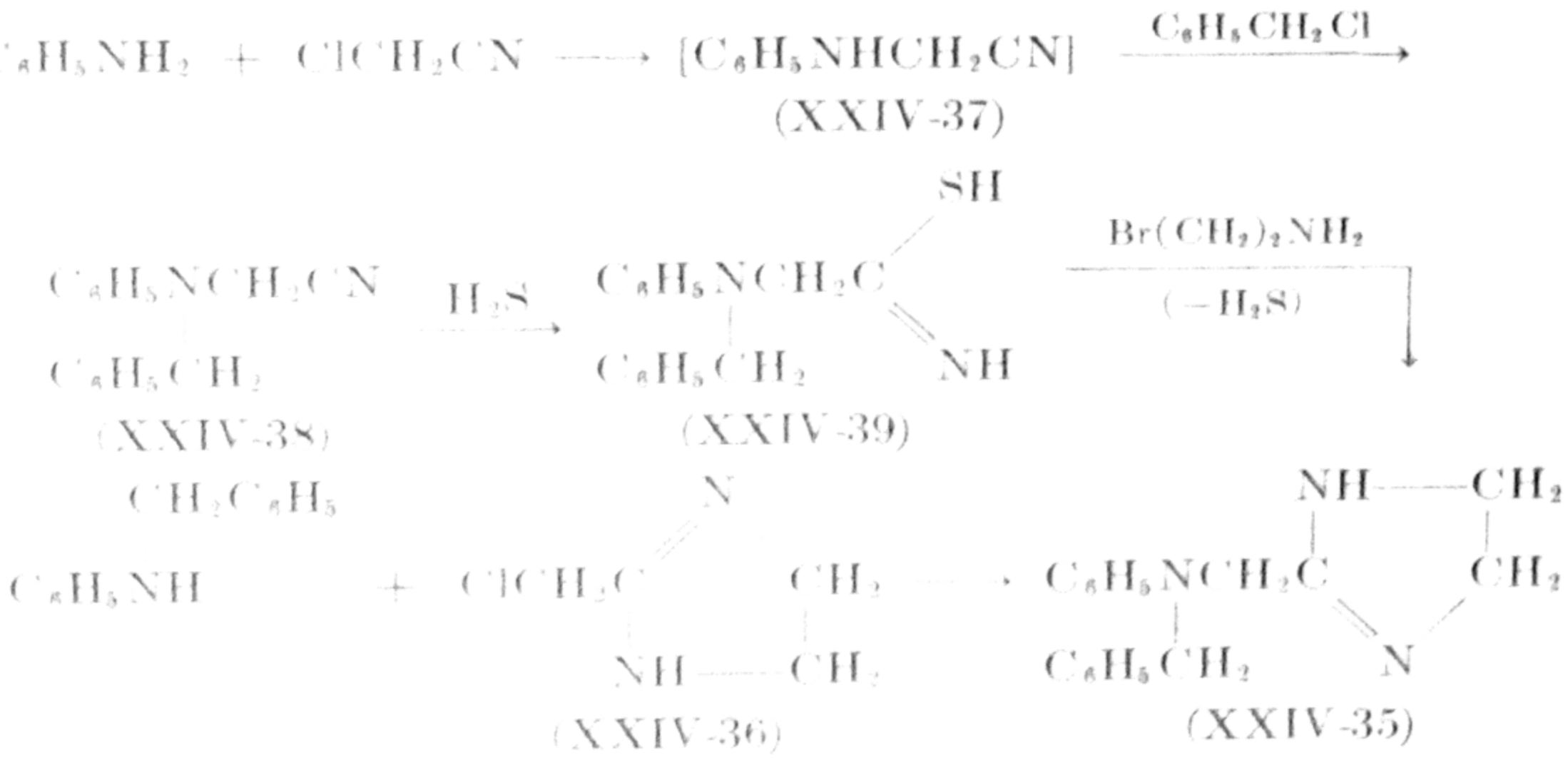


(XXIV-34)

f. Drugs Having Cyclic Basic Chains

(1) *Antistine*

Incorporation of one of the two nitrogen atoms in a heterocyclic system has led to several active and useful antihistaminic drugs. Antistine (XXIV-35) may be regarded as such a compound.[37] It was synthesized from 2-chloromethylimidazoline (XXIV-36) and benzylaniline and has been recommended as a non-irritating agent for local application on the eye. Another synthesis uses the condensation of the (not isolated) anilinoacetonitrile (XXIV-37) with benzyl chloride. The resulting nitrile (XXIV-38) is converted to the thioamide (XXIV-39) which then yields Antistine by condensation with β-bromoethylamine.



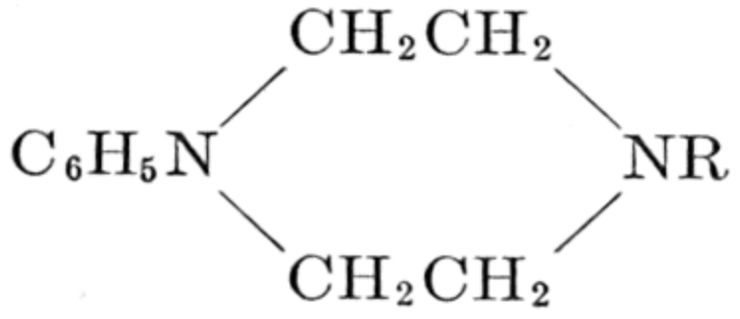
It may be that the imidazoline portion of Antistine contributes to the "steric fitting" of the molecule into the space ordinarily occupied by histamine and thus promotes competition with the latter for cell chemicals. It is as yet unexplained why small amounts of ferric ions potentiate the effect of Antistine. Other antihistaminic agents seem to be influenced in a

[37] Miescher and Riehen, U. S. Pat. 2,449,241 (1948). Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946). Djerassi and Scholz, *J. Am. Chem. Soc.*, **69**, 1688 (1947).

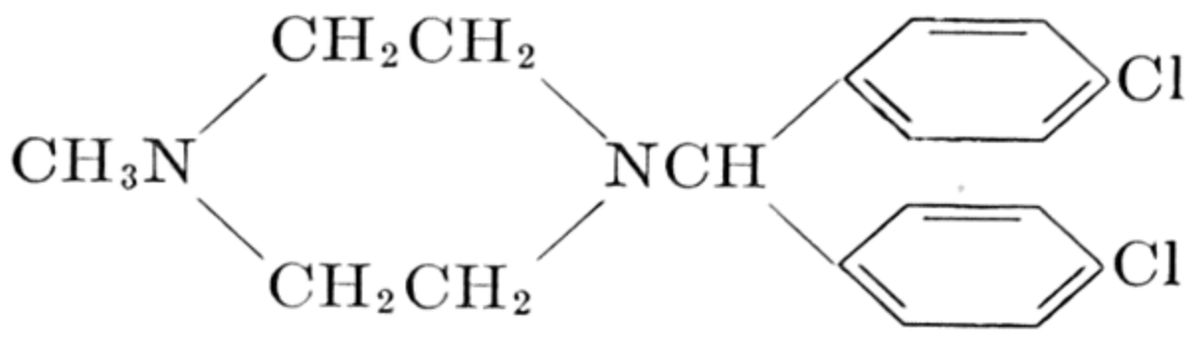
similar manner, and the possibility of pharmacologically active chelated complexes may have to be considered in such cases.

(*2*) *Derivatives of Piperazine*

Another case of including the ethylenediamine chain in a ring is seen in 1-phenyl-4-dimethylaminoethylpiperazine (XXIV-40) which antagonizes up to sixteen lethal doses of histamine. 1-Phenyl-4-(4′-tetrahydropyranyl) piperazine (XXIV-41) acts similarly.[38]

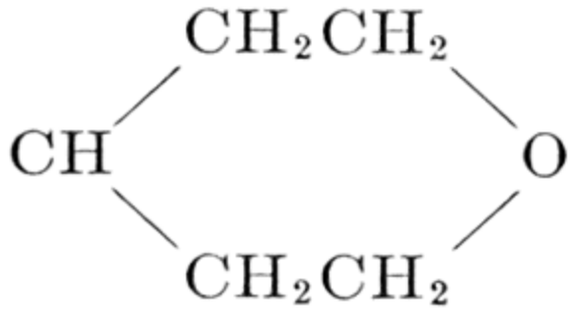


(XXIV-40): R = $(CH_2)_2N(CH_3)_2$



(XXIV-42)

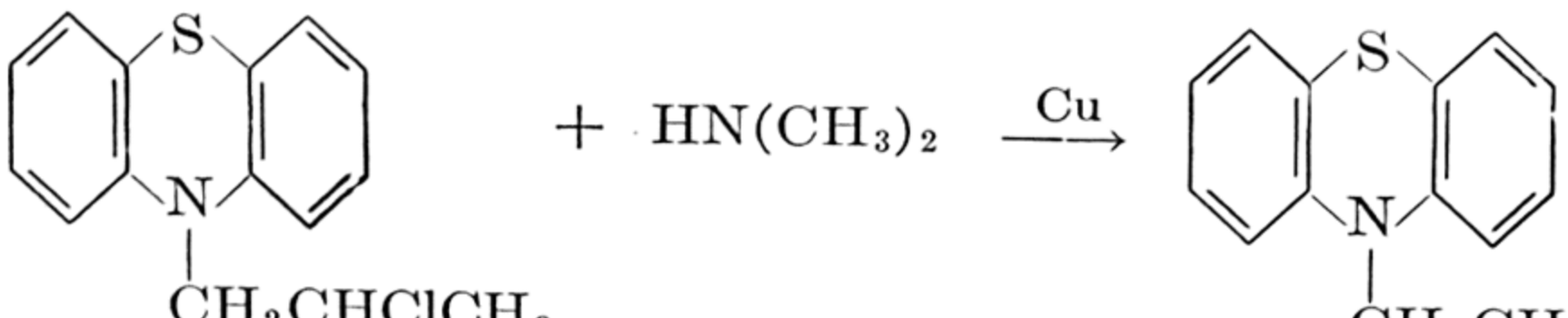
(XXIV-41): R =



1-Methyl-4-(*p*-chlorobenzhydryl) piperazine (XXIV-42) has been tested under the names of Chlorocyclizine or Perazil. It is considered a highly effective drug.[39]

(*3*) *Phenothiazine Derivatives*

Halpern and his coworkers[40] introduced a number of 10-(β-dimethylaminoalkyl) phenothiazine derivatives as potent antihistaminics in which one of the nitrogen atoms of the ethylenediamine chain is part of a heteroring. The compound named Phenergan (XXIV-43) can be prepared from β-(10-phenothiazine) isopropyl chloride and dimethylamine under the influence of copper powder.[41]



(XXIV-43)

[38] Cerkovnikov, Skarica, and Stern; *Arch. Kem.*, **18,** 37, 87, (1946). *Chem. Abstr.*, **42,** 1941, 3394 (1948).

[39] *Chem. Eng. News*, **27,** 1750 (1949). Brown, *Ann. Allergy*, **8,** 32 (1950).

[40] Halpern, *J. Am. Med. Assoc.*, **129,** 1219 (1945). Halpern and Ducrot, *Compt. rend. soc. biol.*, **140,** 361 (1946).

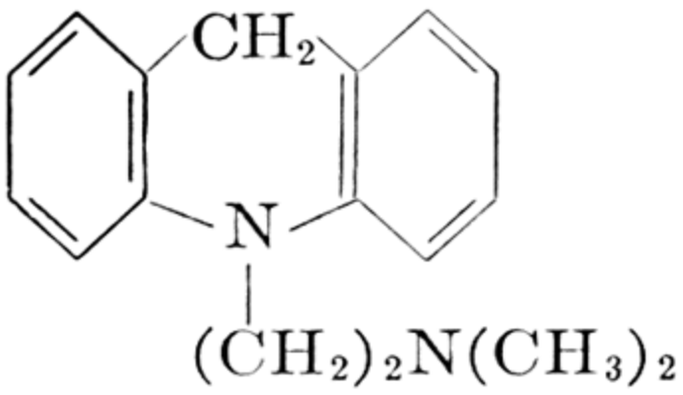
[41] Huttrer, *Enzymologia*, **12,** 293 (1948).

RP 3015 (Table I) is capable of counteracting twenty lethal doses of histamine, while Phenergan which differs from it only by one methyl group, is 75 times as active. This compound is one of the most powerful antihistaminic substances yet discovered. Like other antihistaminics, Phenergan increases the pressor effects of epinephrine.

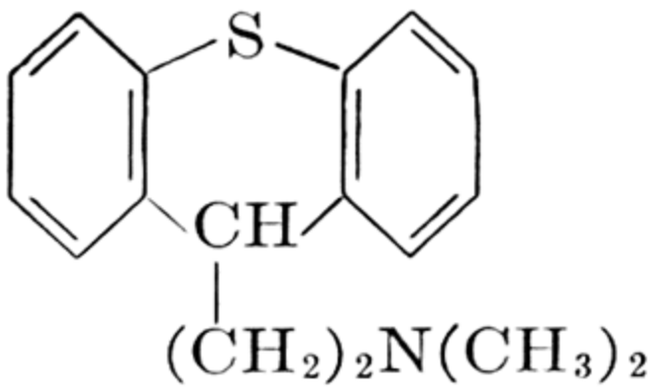
The diethylaminoethyl analog of this phenothiazine derivative (Diparcol) has been found useful in the treatment of Parkinsonism (cf. Chapter XXII). This behavior shows perhaps an overlapping with curariform activity. It is therefore interesting to record that Diparcol is a specific inhibitor of the enzyme pseudocholinesterase[41] which is related in action to, but biochemically different from cholinesterase.[42] 10-(2-Diethylaminopropyl)phenothiazine, a higher homolog of Diparcol, is reported to be even more effective in Parkinsonism.[42a]

It has been hoped that very potent drugs of these series might counteract the effects of gastric stimulation of histamine, but even the most active phenothiazine derivatives do not have this property to a useful degree.

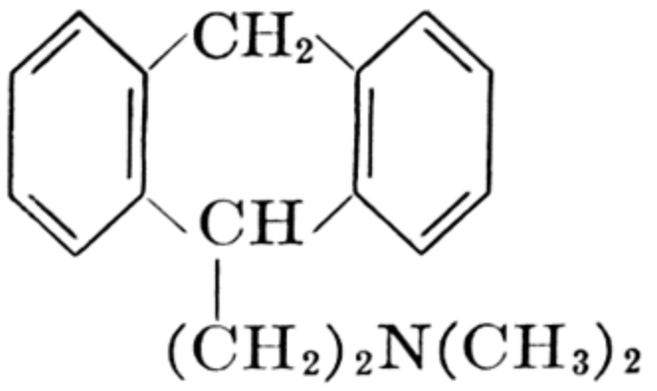
Cyclic analogs of the phenothiazine derivatives seem to be generally capable of protecting guinea pigs against histamine-spray induced anaphylactic shock. If the activity of Benadryl is taken as 1, the following compounds may serve as examples in this comparison:



Activity: 17



(XXIV-44)
Activity: 2



(XXIV-45)
Activity: 4

5. Monoamines

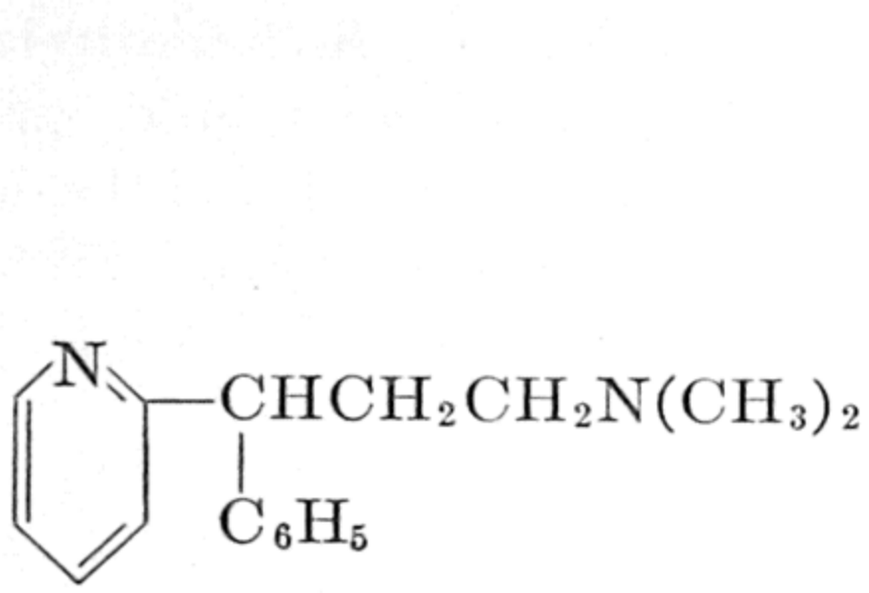
a. Trimeton and Chlor-Trimeton

It will be noted that in the dibenzothiapyran derivative (XXIV-44), and in the 9,10-dihydroanthracene analog (XXIV-45), an ethylenediamine chain is no longer present but only one nitrogen carries the basic function of the molecule. A similar variation of the diamine and ether structures is found in Trimeton, 3-phenyl-3-(2-pyridyl)-dimethylaminopropane (XXIV-46).

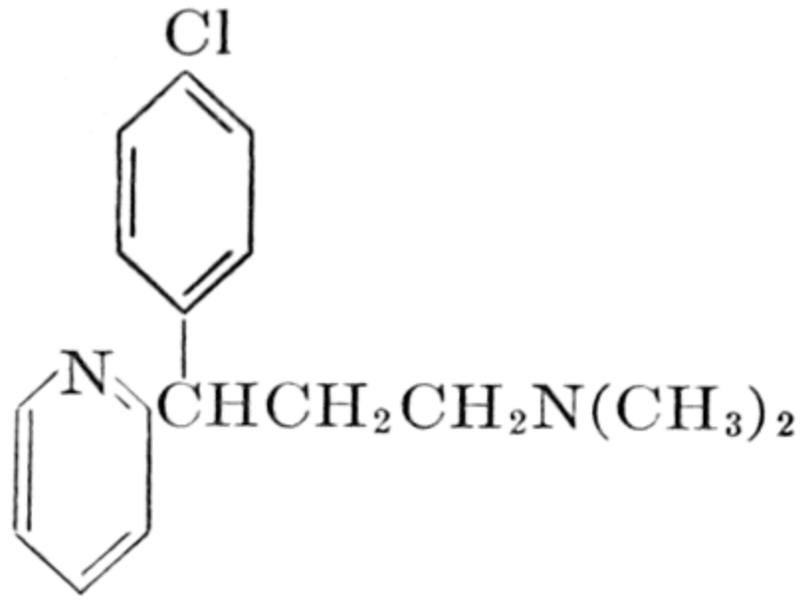
This drug shows antihistaminic action in doses from 0.1 to 2 mg./kg. depending on its mode of administration, and 51 mg./kg. provide up to

[42] Gordon, *Nature*, **162,** 146 (1948). For a classification of cholinesterases, see Augustinsson and Nachmansohn, *Science*, **110,** 98 (1949).

[42a] Sigwald, *Presse. Med.* (Paris) **57,** 819 (1949).



(XXIV-46)



(XXIV-47)

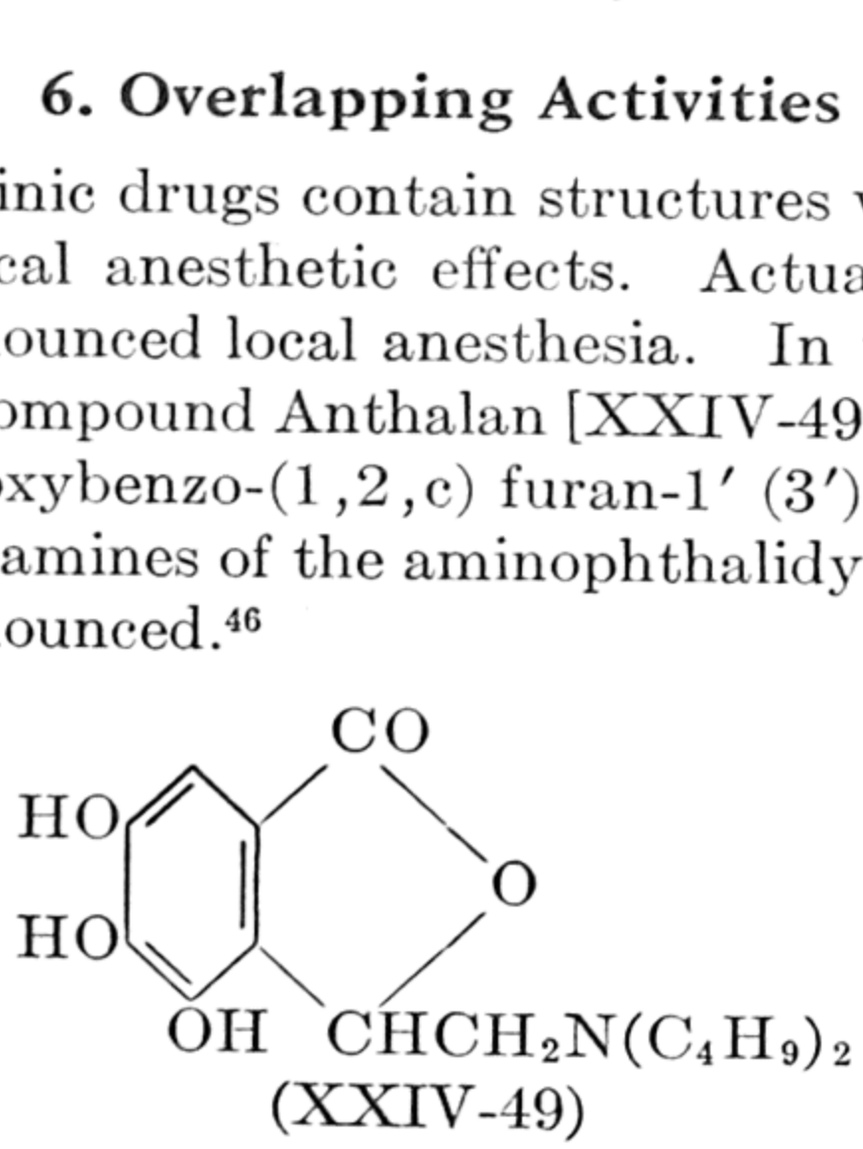
sixteen hours protection from histamine fog in guinea pigs. The *p*-chloro compound (XXIV-47) is even more active. It is said to have 50 times the activity of some of the other widely used antihistaminic drugs.[43, 44]

b. Thephorin

In Thephorin (XXIV-48), the alkylamine side chain is part of a tetrahydropyridindene ring.[45] The LD_{50} of this drug is approximately the same as that of Benadryl or Pyribenzamine but it is reported more potent and less toxic than these drugs. It has been used widely in pediatric practice[45] and has been tested in paralysis agitans. Thephorin is supposed to suppress secretion of gastric hydrochloric acid. It also prevents swelling from bee venom, and is supposed to act favorably in sea sickness.

6. Overlapping Activities

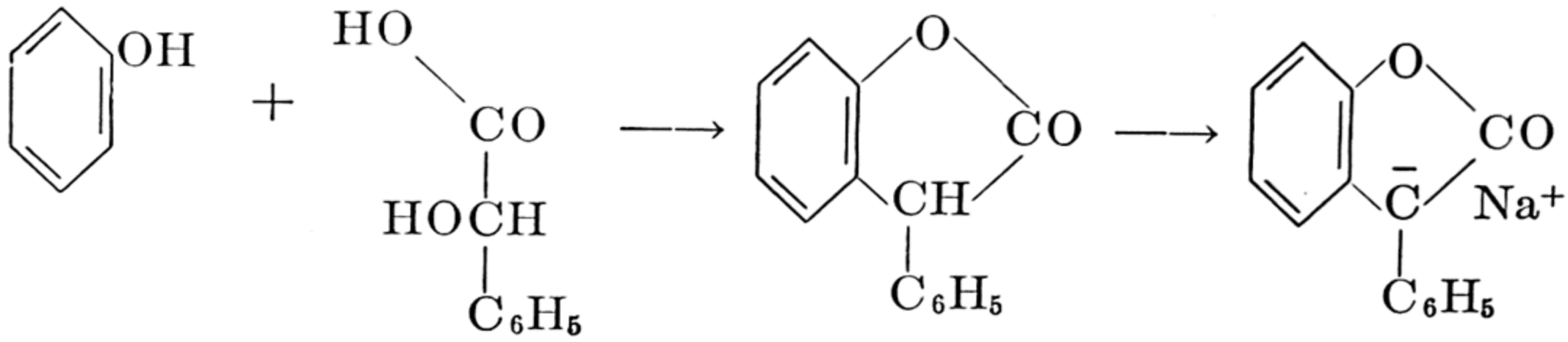
Many antihistaminic drugs contain structures which may be expected to elicit pressor, or local anesthetic effects. Actually, many useful antihistaminics cause pronounced local anesthesia. In the case of the weakly active antihistamine compound Anthalan [XXIV-49; 3′-di-(*n*-butyl)aminomethyl-4,5,6-trihydroxybenzo-(1,2,c) furan-1′ (3′)-one] the structural relation to the analgetic amines of the aminophthalidylalkane series (Chapter XI) is especially pronounced.[46]



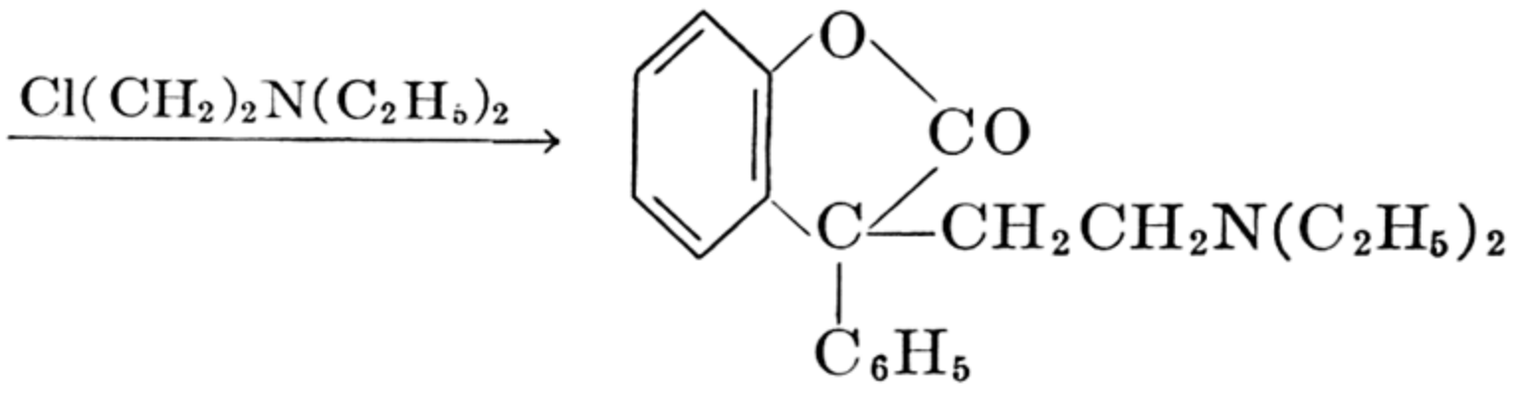
(XXIV-49)

[43] cf. Huttrer, *Experientia*, **5**, 53 (1949).
[44] Sperber, Papa, Schwenk, and Sherlock, *J. Am. Chem. Soc.*, **71**, 887 (1949). Labelle and Tislow, *Federation Proc.*, **7**, 236 (1948); **8**, 338 (1949).
[45] Plati and Wenner, U. S. Pats. 2,470,108 and 2,470,109 (1949).
[46] Ghiselin, *Bull. N. Y. Acad. Med.*, **22**, 320 (1946). Schwarzschild, *N. Y. State J. Med.*, **46**, 1563 (1946).

A similar relation exists for the drug Amethone, 3-(β-diethylaminoethyl)-3-phenyl-2-benzofuranone (XXIV-50). The compound prevents histamine shock in guinea pigs in doses of 7 mg./kg. It is synthesized by condensing phenol with mandelic acid in sulfuric acid solution, and attaching the side chain to the sodio derivative of the lactone (XXIV-51).[47]

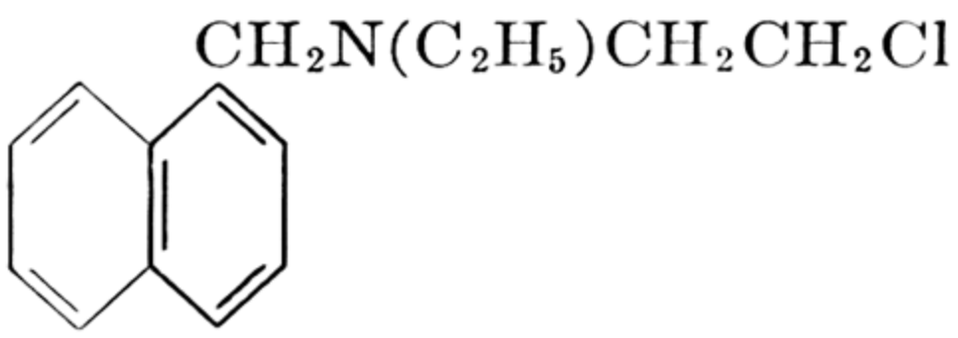


(XXIV-51)

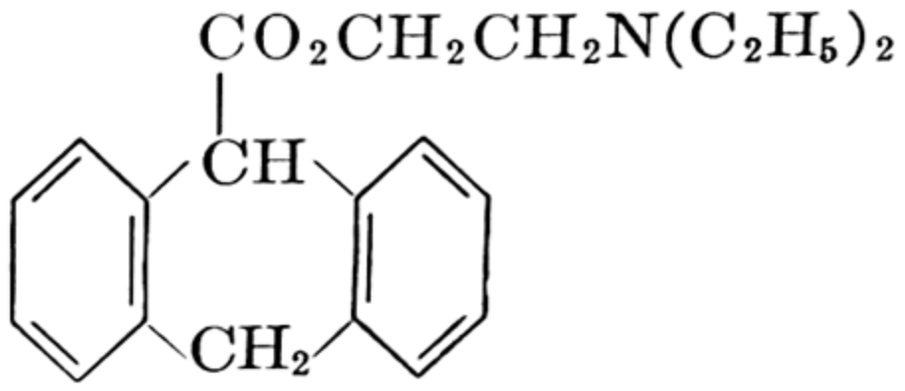


(XXIV-50)

Much speculation has centered around the possibility that antihistaminic drugs may have a mode of action related to that of epinephrine, a powerful agent in relieving acute asthma. However, certain antihistaminics of the Fourneau series actually antagonize sympathomimetic effects of epinephrine. Moreover, various adrenergic blocking agents, especially α-naphthylmethyl-ethyl-β-chloroethylamine (XXIV-51), are more effective than epinephrine in preventing histamine as well as anaphylactic shock in guinea pigs.[48]



(XXIV-51)



(XXIV-52)

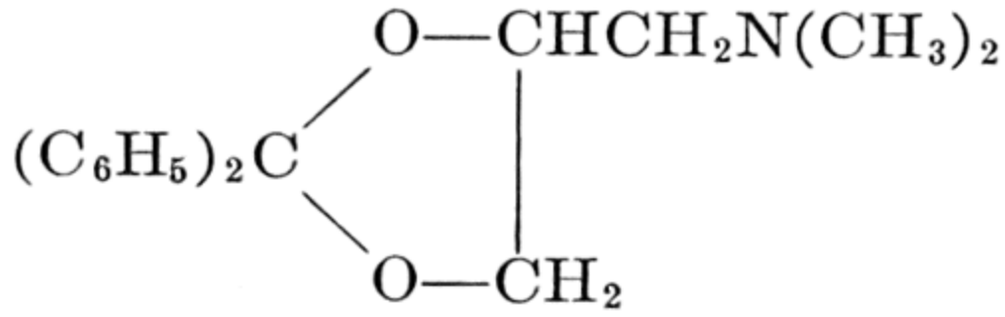
That overlapping of sympatholytic, antispasmodic and antihistaminic properties has been observed in many compounds, has been mentioned in other Chapters. Thus, diethylaminoethyl 9,10-dihydroanthracene-9-carboxylate[49] (Hydrillin, XXIV-52), β-diethylaminoethyl phenylpropylacetate

[47] Weston and Brownell, Am. Chem. Soc. Meeting, Atlantic City, 1946.
[48] Loew, *Physiol. Revs.*, **27,** 542 (1947).
[49] Cusic, U. S. Pat. 2,450,122 (1948). Hambourger, Freese, Winbury, and Michiels, *J. Pharmacol. Exptl. Therap.*, **94,** 367 (1948).

(XXIV-53, Propivane), Demerol (Chapter XI), and other typical antispasmodic esters antagonize the spasmogenic action of histamine on intestinal muscle.[50] The 1,3-dioxolane (XXIV-54) is a potent inhibitor of acetylcholine and potentiates Decapryn in sensitized guinea pigs.

$$C_6H_5CH(C_3H_7)CO_2CH_2CH_2N(C_2H_5)_2$$

(XXIV-53)



(XXIV-54)

The whole pharmacological question of the interdependence of epinephrine (adrenergic), acetylcholine (cholinergic) and histamine activities needs re-examination. There is a growing tendency to believe that the antagonism or occasional synergism of these three natural agents may be due to their competition for the *same* cell receptors (enzymes), and that drugs mimicking or antagonizing their effects enter into this competition and thus alter the natural equilibria of the reactions at the receptor sites. It is also possible that the adrenal cortex hormone, Cortisone (Chapter XXIX) acts by an antihistamine-like mechanism. Cortisone appears to prevent the formation of histamine from proteins and thereby to counteract the fibrosis in aging tissue which is promoted by histamine. There is evidence that ACTH (Chapter XXIX) is essentially an antiallergic factor since it removes the symptoms of some diseases without curing the disease. Even vitamin B_{12} has been shown to protect guinea pigs against serum shock,[51] and adenosine-5-monophosphate to be effective against intense itching (pruritus).[52]

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Huttrer, *Enzymologia*, **12,** 277 (1948).
Haley, *J. Am. Pharm. Assoc.*, **37,** 383 (1948).
Viand, *Produits Pharmaceutiques*, **2,** 53 (1947).
Loew, *Physiol. Revs.*, **27,** 542 (1947).
Feinberg, *J. Am. Med. Assoc.*, **132,** 702 (1946).

[50] Pfeiffer and Loew, *Ann. Rev. Physiol.*, **9,** 651 (1947).
[51] Traina, *Nature*, **166,** 78 (1950).
[52] Kennedy, *N. Y. State J. Med.*, **50,** 1609 (1950).

CHAPTER XXV

Diagnostic Agents

Diagnostic chemicals are used as an aid in the clinical diagnosis of disease which must precede any plan for restoration of normal health. Some of the compounds have been designed specifically as diagnostic tools and have no other use. Others combine with their application in diagnosis certain properties which make them also valuable as therapeutic agents. The main function of diagnostic agents is to demonstrate abnormalities in structure or impairment of the functions of the body organs.[1]

Any compound which causes a color reaction, or which gives an insoluble precipitate with a chemical found in the body will be helpful in diagnosis. Complex cupric ions which are converted to insoluble cuprous oxide by reducing saccharides are used to recognize the presence of glucose in the urine or the blood, acetic acid coagulates proteins in the urine and points thereby to impaired kidney function. Serological reactions determining blood groups, types of infections, or the presence of antibodies, and even the dyestuffs used to stain samples of invading pathogens under the microscope could be classified as diagnostic tools. The chemicals producing the innumerable qualitative and quantitative reactions of the clinical laboratory all belong in this group. However, the term diagnostic agent has been reserved, by tradition, to a small number of compounds which have a more closely circumscribed mission. They are, first, the radiopaques which cast shadows on X-ray film when present in organs which could otherwise not be made visible by roentgenography. A second group comprises compounds which are excreted at such a rate that they permit evaluation of the proper or impaired functioning of internal organs, especially the kidney and the liver. In the last few years, radioactive isotopes have found limited use in the diagnosis of circulatory and metabolic dysfunction.

I. RADIOPAQUES

1. Inorganic Compounds

Inorganic radiopaques or X-ray visualization agents are used to outline the organs of the alimentary canal, the esophagus, stomach and the intestines. The materials distribute themselves over every surface, fold,

[1] Avis, *Am. Profess. Pharmacist*, **14**, 325, 333, 431 (1948).

ulcer, tumor or other structure and cast a contrasting shadow which makes the organs visible for roentgenography or fluoroscopy.

Barium sulfate, thorium dioxide and bismuth oxides, made into stable suspensions, are the most widely used agents in this group. The suspensions are either administered by mouth, or as retrograde enemas for the visualization of the bowel. Because the heavy inorganic particles soon settle out even of the most finely divided suspensions, some roentgenologists prefer iodinated organic compounds which are, in addition, even more opaque to X-rays.

2. Iodinated Organic Compounds

The discovery that iodinated organic compounds can be used as X-ray visualization diagnostics stems from studies of Binz.[2] All of them contain iodine atoms in relatively firm covalent linkages, and release of iodide ions is not to be expected readily. Nevertheless, caution is usually advocated against their use in tuberculosis and thyroid diseases which are adversely affected by iodide ions.

The organs through which the injected materials pass primarily are the blood vessels, the heart, the gall bladder, the kidney, bladder, and urethra. Among the requirements of a satisfactory radiopaque are rapid excretion and lack of systemic absorption, apart from low toxicity and the ability to produce adequate opaqueness. The clinically used drugs of this series are often excreted within thirty to one-hundred minutes after injection, and the choice of iodinated compounds is now wide enough to permit the application of exacting standards.

The screening of iodinated radiopaques can be carried out in mice. The animals are autopsied, and the iodine content of their gall bladder is determined.[3]

From a chemical point of view it seems offhand virtually impossible to fulfill the solubility requirements of X-ray diagnostic iodine compounds for intravenous injection. In order to cast deeply contrasting shadows, a high percentage of iodine, preferably over 50%, is desirable. That puts the molecular weight of a compound of even a modest molecular formula above 300, since a high percentage of iodine can often be achieved only by introduction of at least two atoms of the element. Compounds having molecular weights of this magnitude can barely be expected to be highly soluble in neutral aqueous media. Yet, the roentgenologist prefers substances with a solubility of at least 40%. Large amounts of the drug have to be administered (30 grams or more in one injection of Skiodan), and if the solubility of

[2] See Binz, *Angew. Chem.* **48,** 425 (1935). Maier-Bode and Altpeter, *Das Pyridin und seine Derivate,* Wilhelm Knapp, 1934, pp. 138–141.

[3] Dews, Tornaben, Lang, Norton, and deBeer, *Federation Proc.*, **8,** 316 (1949).

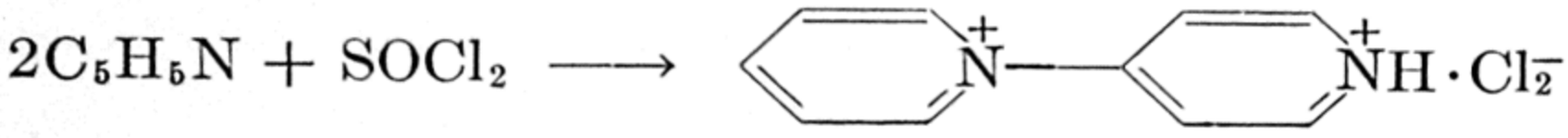
the agent would be around 10 or 15%; the large volumes of fluid would upset the water balance of the body and obscure the diagnosis. Therefore, much work has been done to convert slightly soluble highly iodinated compounds into highly water-soluble physiologically inert derivatives. Glucosides and esters of sugar acids and similar hydroxylated materials have been subjected to extensive trials, but the really valuable contribution to the solubility problem was the discovery that the ethanolamine salts of polyhalogenated acids whose alkali salts are frequently sparingly soluble, can be dissolved in water at high concentrations.

This finding has also been applied to quite unrelated fields. 2,4-Dichlorophenoxyacetic acid, 2,4,6-trichlorophenoxyacetic acid, chlorinated naphthoxyacetic acids and similar substances useful as plant hormones are also too insoluble as such or as their sodium salts, and cannot even be sprayed at the high dilutions necessary for optimum hormonal stimulation. Here again, the salts of ethanolamines are readily soluble in water.

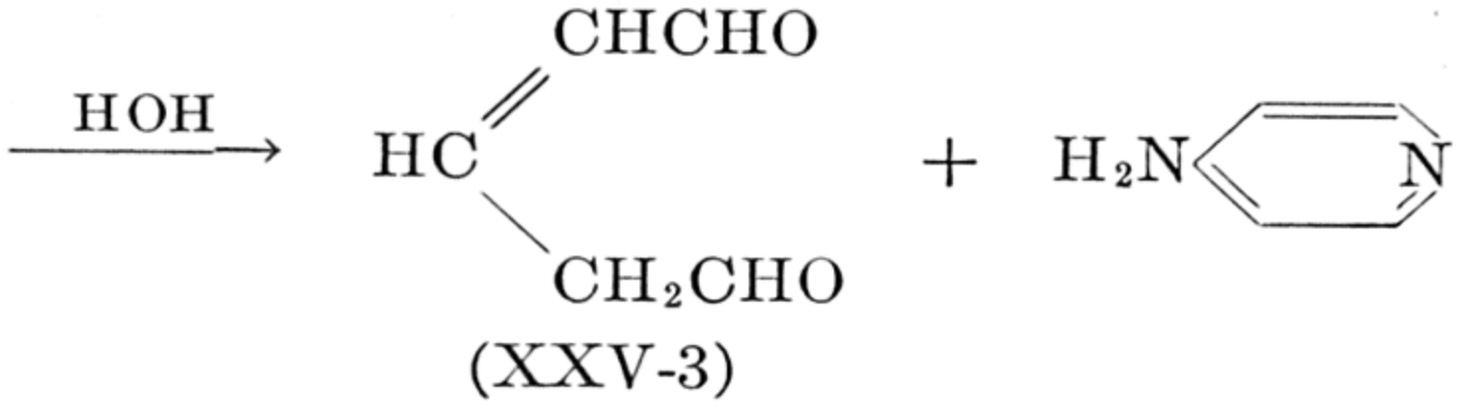
The difficulty of dissolving iodinated compounds in a minimum of water is greater for aromatic and heterocyclic compounds than in the aliphatic series. Sodium iodomethanesulfonate (Skiodan, ICH_2SO_3Na) dissolves satisfactorily at high concentrations. Radiopaques for which high solubility has not been achieved may still retain roentgenographic usefulness by other routes of administration. They may be given orally in syrups, or injected into the renal pelvis through a ureteral catheter for visualization of the urinary tract. However, the parenteral route of injection remains the preferred working method.

One of the earliest and still most successful organic iodinated radiopaques has been diethanolammonium 3,5-diiodo-4-pyridone-1-acetate (Diodrast, Iodopyracet, XXV-1). It is synthesized from pyridine which, when heated with thionyl chloride, yields 4-pyridiniumpyridine chloride hydrochloride (XXV-2). The latter can be hydrolyzed to glutacondialdehyde (XXV-3) and 4-aminopyridine which is then converted to γ-pyridone (XXV-4) by treatment with acids. Iodination, followed by condensation with chloroacetic acid, yields the free acid which is then neutralized with diethanolamine.

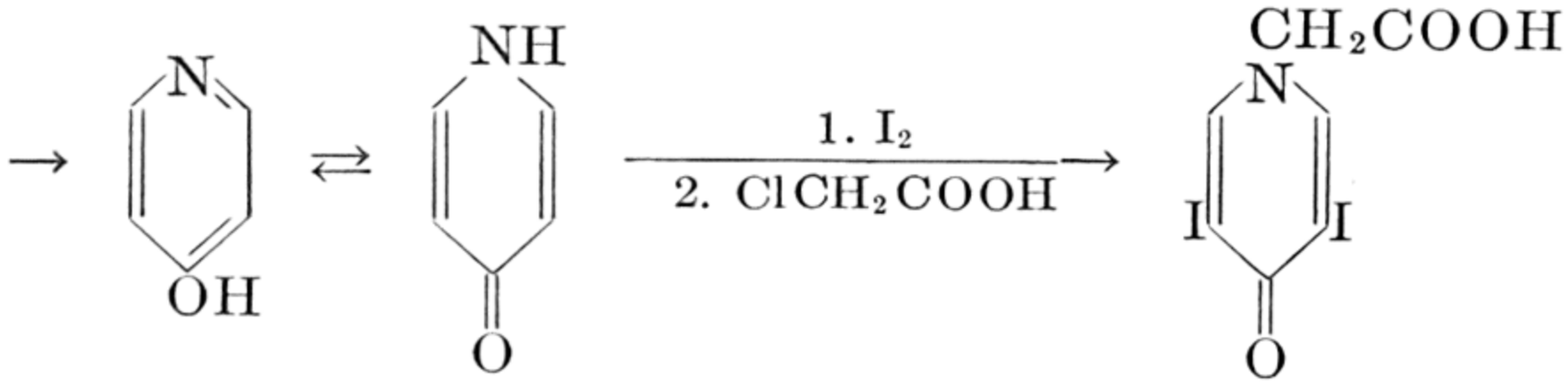
In a similar way, sodium 2-oxo-5-iodopyridine-1-acetate (Uroselectan, Iopax) was synthesized but it has been superseded by a safer urographic agent, the salt of 1-methyl-3,5-diiodochelidamic acid (Neo-Ipax, Uroselectan B, XXV-5). Its preparation starts from γ-pyridone-2,6-dicarboxylic acid (chelidamic acid, XXV-6) which can be obtained by ammonolysis of chelidonic acid (XXV-7). Chelidamic acid is iodinated, and the hydrogen on the cyclic nitrogen atom replaced by a methyl group.



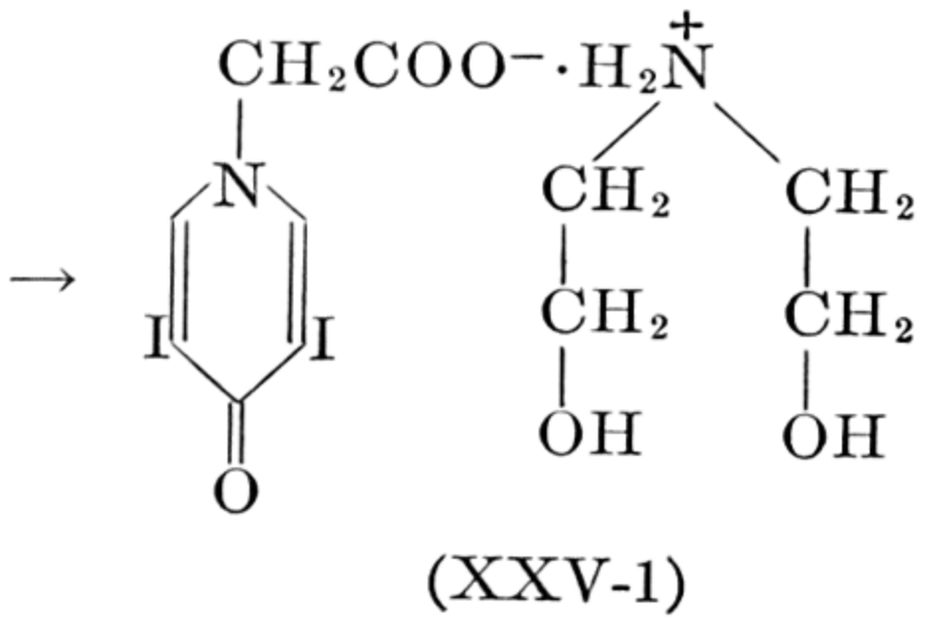
(XXV-2)



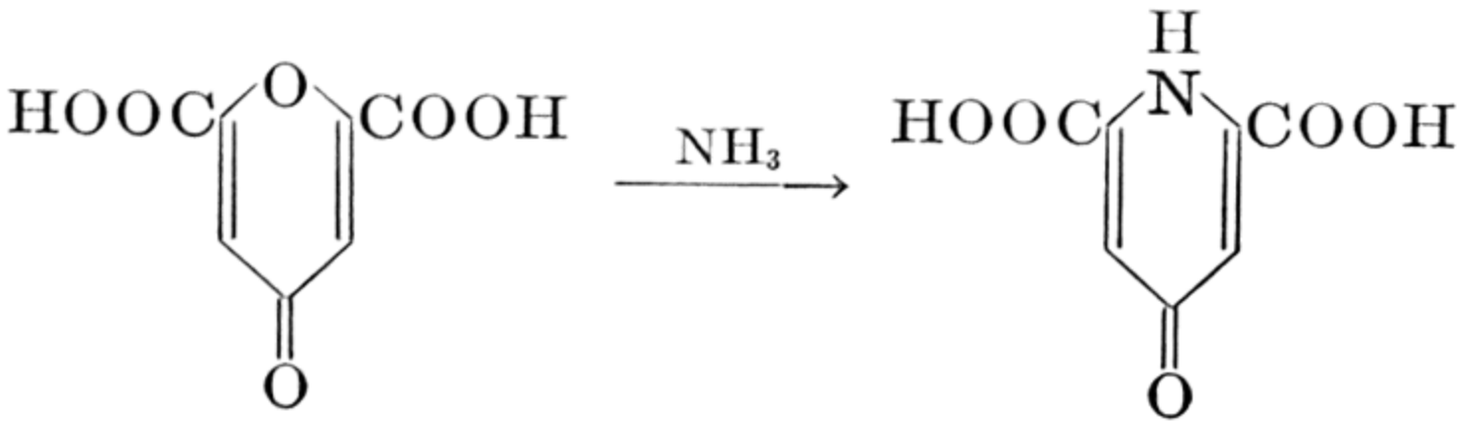
(XXV-3)



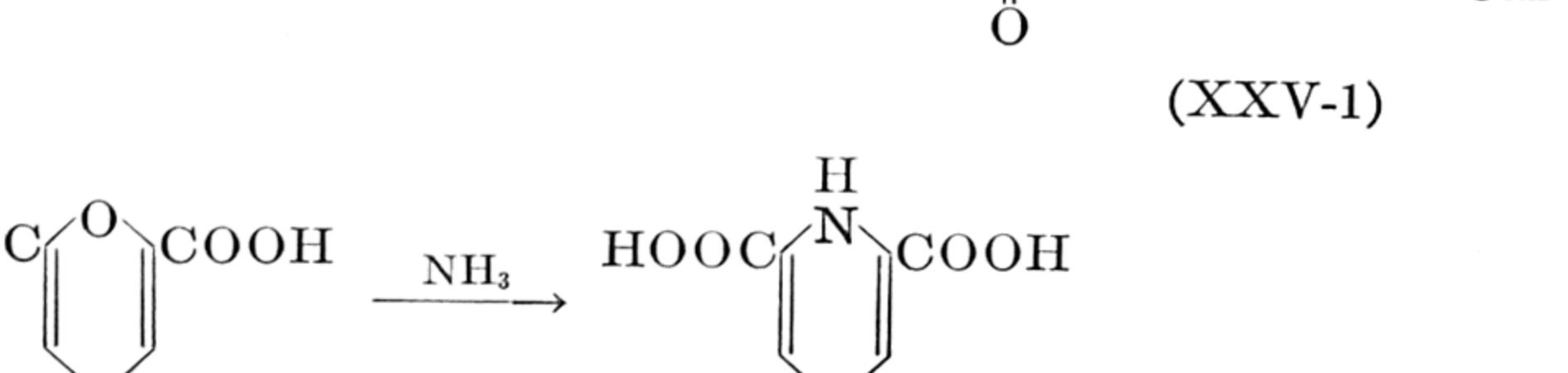
(XXV-4)



(XXV-1)

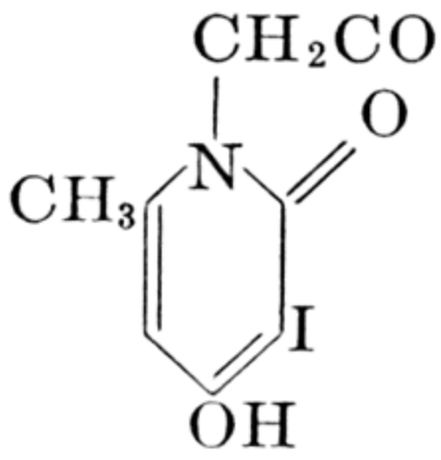


(XXV-7) (XXV-6)

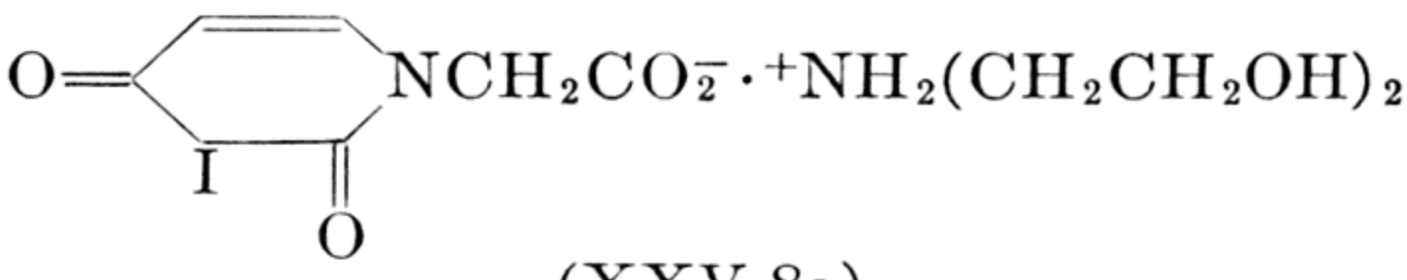


(XXV-5)

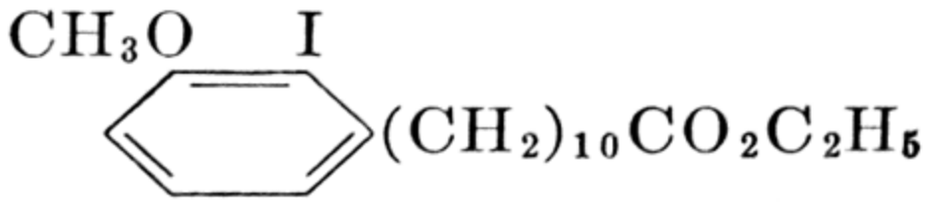
Another pyridone, the diethanolammonium salt of 3-iodo-4-hydroxy-6-methyl-2-pyridoneacetic acid (XXV-8) is used under the name of Rayopake as a non-toxic and readily absorbable agent. It is readily excreted, and this eliminates the need to aspirate the bladder or urethra after its use. A similar salt (XXV-8a) has been recommended for hysterosalpingography.[3a]



(XXV-8)

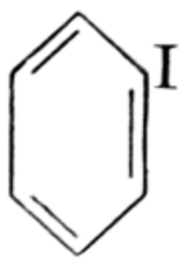


(XXV-8a)



(XXV-8b)

Among well tolerated iodinated aromatic derivatives are ethyl 11-(*p*-iodophenyl) undecanoate[3b] which is used for myelography, and the *o*-iodo-*m*-methoxy analog (XXV-8b). The latter gives sharp and uniform visualization of the human spinal canal.[3c]



(XXV-9)

Sodium *o*-iodohippurate (Hippuran, XXV-9) is prepared by treating *o*-iodobenzoyl chloride with glycine. It is an effective diagnostic aid in urography. Sodium 3-acetamido-2,4,6-triiodobenzoate (Urokon) is also widely used.

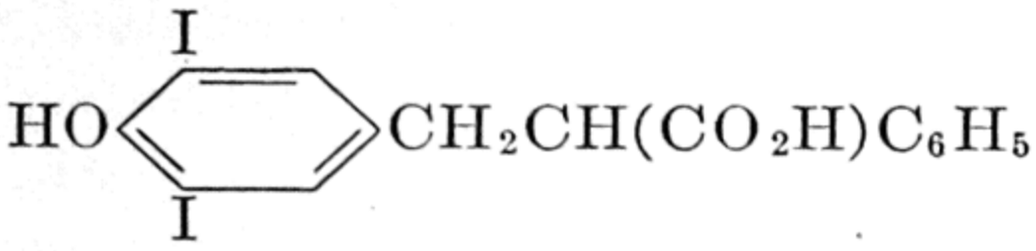
Several of the agents discussed above can serve also in X-ray visualization of the lungs and of the gall bladder. However, oral administration of certain other substances appears to give better results for the latter purpose (choleography, cholecystography).

[3a] Schnider, U. S. Pat. 2,212,187 (1940); Norment, *Am. J. Obst. Gynecol.*, **49,** 253 (1945); Montgomery and Lang, *ibid.*, **51,** 702 (1946).

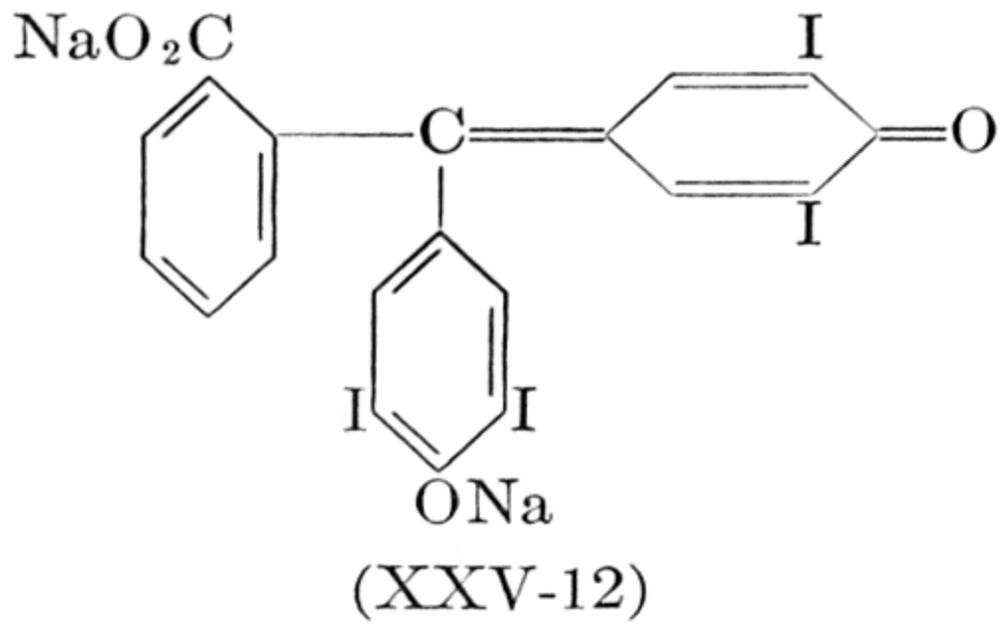
[3b] Strain, Plati and Warren, *J. Am. Chem. Soc.*, **64,** 1436 (1942).

[3c] Papa, Schwenk and Klingsberg, *J. Am. Chem. Soc.*, **72,** 2623 (1950).

A widely used cholecystographic agent is α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl) propionic acid (Priodax, XXV-10). Although very toxic when injected parenterally, the compound is well tolerated and readily eliminated after oral ingestion.[4] It should not be used in acute nephritis



(XXV-10)



(XXV-12)

and uremia. A large number of related iodinated diphenylaliphatic acids have been found without value.

A similar amphoteric compound, 2-(3,5-diiodo-4-aminophenyl)-3-phenyl-propionic acid (XXV-11) has been recommended as a radiopaque agent for gall bladder diagnosis.[5]



(XXV-11)

The other most important agent for cholecystography is tetraiodophenolphthalein (XXV-12) which is most conveniently obtained by direct iodination of the parent indicator. It is used as the sodium salt under various names such as iodophthalein, Iodikon, Phentetiothalein etc.

3. Iodinated Vegetable Oils

Iodinated oils are prepared by adding iodine to the double bonds of unsaturated vegetable glycerides. The resulting viscous products such as Lipidol, an iodized poppy seed oil, are injected as contrast media in the diagnostic visualization of lesions and tumors of the spinal cord, the bronchies, sinuses, lungs, seminal vesicles and female sex glands. The oils of sesame, rape and poppy seeds and others may be used. They have virtually no pharmacological effects but their viscosity is a potential source of danger; they have to be injected under high pressure, are absorbed only slowly, and droplets floating off into the circulatory capillaries of vital centers can cause embolism.

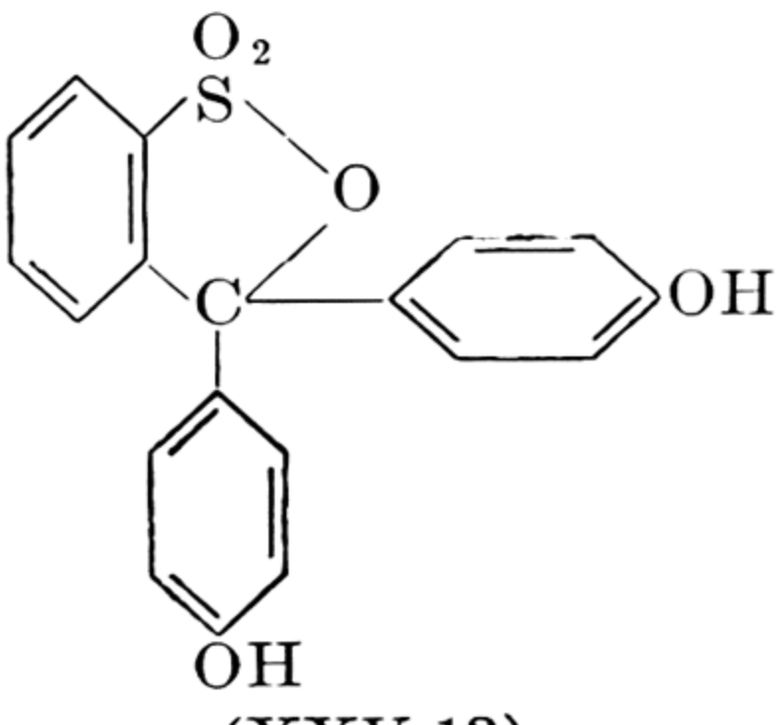
[4] Dohrn and Diedrich, U. S. Pat. 2,345,384 (1944).

[5] Lewis, Pratt, Homiller, Tullar, and Archer, *J. Am. Chem. Soc.*, **71,** 3749 (1949). Hope and Archer, *Federation Proc.*, **8,** 303 (1949).

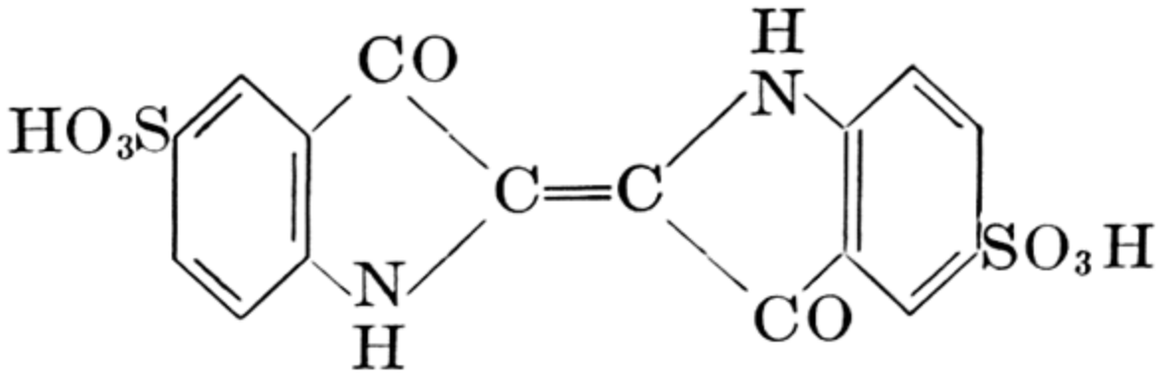
These drawbacks can be countered in two ways. One is to add other halogens along with a sufficient percentage of iodine to the double bonds and thereby to decrease the viscosity of the products. Iodochlorol is an example of such materials. Even bromine alone, without any iodine, has furnished a satisfactory radiopaque in brominated olive oil (Brominol). The alternative procedure is to choose esters other than glycerides for iodination. Ethyl diiodobrassidate, $CH_3(CH_2)_7CHICHI(CH_2)_{11}CO_2C_2H_5$, is a useful diagnostic oil of this type. Synthetic analogs have also been successfully employed. A mixture of isomeric iodophenylundecylenic acids (Pantopaque) can be emulsified with water and injected; it is valuable for roentgenological visualization of internal mucosas. Ethyl iodophenylundecylate is used under the name of Myodil as a contrast agent for myelography.

II. DIAGNOSTIC AGENTS FOR RENAL AND HEPATIC FUNCTION

Diseases of the kidney may be diagnosed and followed by evaluating the capacity of the organ to carry out its normal functions. These include the ability of the kidney to concentrate or dilute urine, to eliminate materials introduced as diagnostic aids, and to excrete waste products (e.g. urea) as measured by renal clearance tests.[6] A combination of tests for these functions will give the diagnostician a fair picture of the condition of the kidney.



(XXV-13)



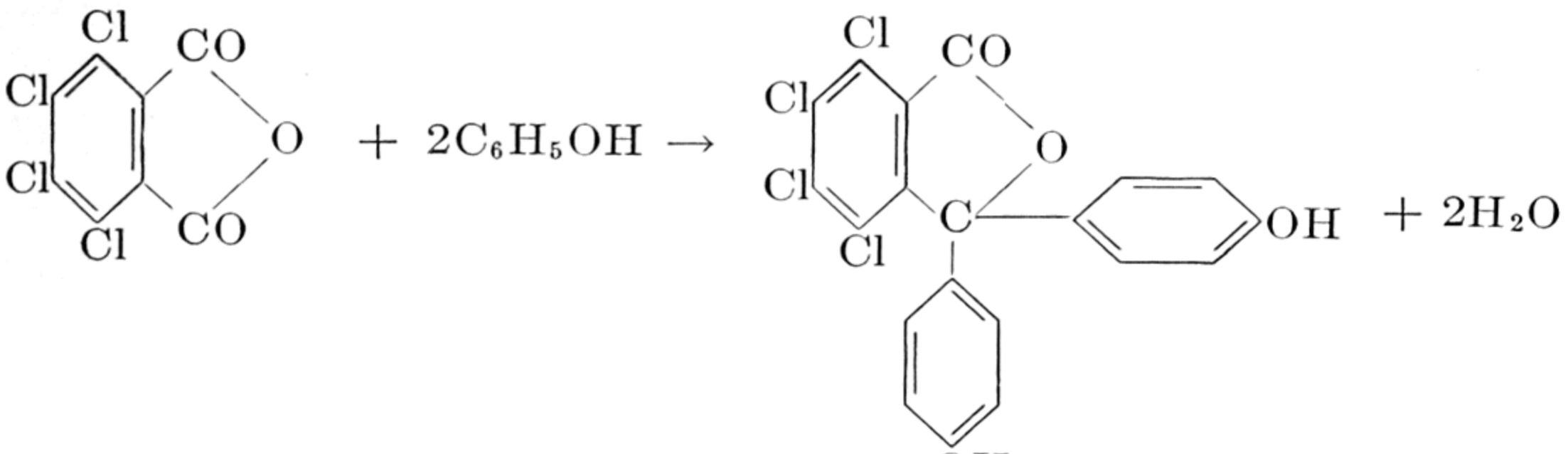
(XXV-14)

The dyestuffs Phenol Red (phenolsulfonphthalein, XXV-13), the blue dye Indigocarmine (indigodisulfonic acid, XXV-14) and methylene blue (XXXV-20) provide an excellent means of testing the functional capacity of the kidney.[7] Since they are readily absorbed, essentially harmless, and excreted almost entirely through the kidney, they can be detected in the urine five to ten minutes after parenteral injection. By determining

[6] Freyberg, *J. Am. Med. Assoc.* **105,** 1575 (1935).
[7] Meyer and Jacobsen, *Organic Chemistry.* de Gruyter, Berlin, 1920, p. 313.

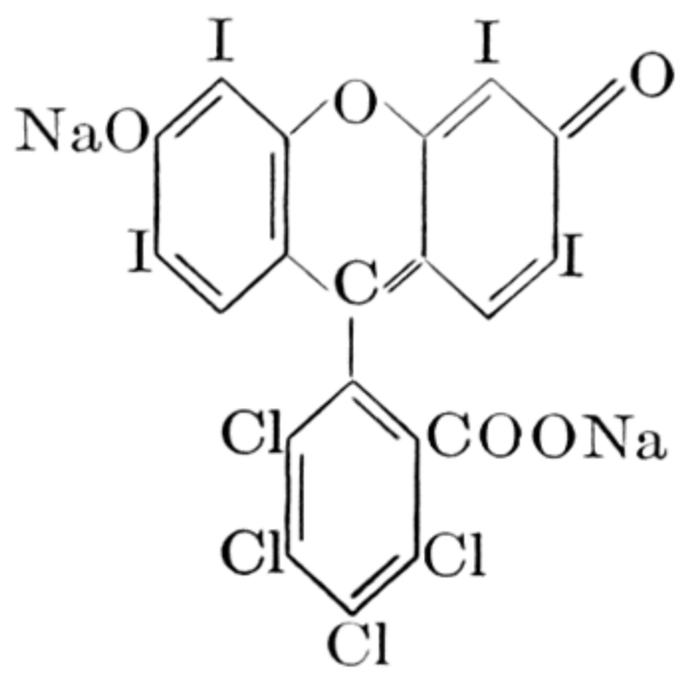
colorimetrically the percentage of the dye excreted by the normal kidney, abnormal values permit conclusions concerning renal disorders.

In a similar manner, hepatic function can be estimated. Certain dyestuffs are eliminated from the blood chiefly by the liver and excreted in the bile. The time needed before the dye is removed from the blood by the liver serves as a diagnostic means of the functional capacity of the organ. The dye is injected intravenously into one arm, blood is withdrawn from the other arm after given intervals and the plasma is analyzed colorimetrically for the amount of dye remaining in the circulation. Since the liver empties the dyestuff by way of the gall bladder into the duodenum, tests analyzing the percentage of dye in the feces and intestinal contents have also been set up.



(XXV-15)

The dyes used for hepatic functional tests are tetrabromo- or tetraiodophenolphthalein (XXV-12) as well as the tetrachlorophenolphthalein (XXV-15) resulting from the interaction of tetrachlorophthalic anhydride and phenol.



(XXV-16)

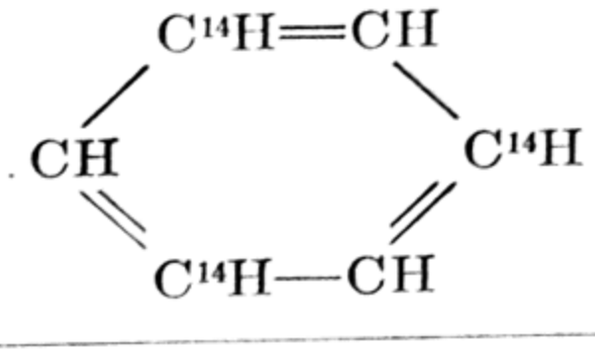
Rose Bengal, the disodium salt of tetraiodotetrachlorofluorescein (XXV-16) is also an excellent indicator of liver function.

III. RADIOACTIVE COMPOUNDS

Compounds containing radioactive isotopes have become more readily available with the development of cyclotrons, betatrons and other machines in which bombardment of chemicals with atomic particles can be carried out. Fairly large quantities of radioactive elements and their compounds are obtained from the wastes of the fission products in atomic piles, and have been made available to chemists, physicists and medical scientists for experimentation and for possible use in medicine. The factors limiting the use of radioactive compounds are the high price of the materials, the danger from uncontrolled radiation to the patient and the attending personnel, and the lack of comprehensive information about such compounds which is overcome only slowly.

Diagnostic and therapeutic applications of radioactive compounds are closely interwoven. Even if a compound is administered solely for the destructive effect of its radiation on neoplastic tissue, its accumulation in that tissue and its excretory path will be followed closely with Geiger counters and other electrometric instruments. Therefore both a few diagnostic and therapeutic uses of radioactive compounds will be considered on these pages.

TABLE I. Some Radioactive Compounds in Medicine

Name	Formula
Radiosodium Chloride	$Na^{24}Cl$
Sodium Radioiodide	NaI^{131}
Radiocarbon Dioxide	$C^{14}O_2$
Radioiron Sulfate	$Fe^{59}SO_4$
Radiocobalt Nitrate	$Co^{55\text{-}58}(NO_3)_2$
Sodium Radiophosphate	$Na_2HP^{32}O_4$
Radioactive Acetic Acid	$C^{14}H_3COOH$ or $CH_3C^{14}OOH$
Radioactive Chloroform	$C^{14}HCl_3$
Radioactive Benzene	

Several inorganic salts and structurally simple organic compounds possessing radioactivity are available from the sources mentioned above. Those that have attracted medical attention are listed in Table I. Such compounds as benzene and acetic acid are not in themselves of medicinal interest but have served as starting materials in many syntheses of radioactive drugs. It is to be understood that none of the compounds in Table I

contain all of their labeled elements as radioactive isotopes. The atoms labeled with the isotopic weights contain usually only a small percentage of the radioactive isotopes while the remainder of the particular "enriched" element has the normal atomic weight. However, the radiation of even the small fraction of radioactive atoms can be picked up with sensitive Geiger counters.

The study of organic radioactive medicinals has had, so far, a purely biochemical purpose. Absorption, distribution, excretion and metabolic changes of a labeled drug can be followed in the animal, and these investigations have confirmed many previous observations, and obliterated others concerning the fate of the drug in the organism. Since this problem holds virtually all the answers a medicinal chemist has asked for generations, and which could guide him in the future, a considerable number of radioactively labeled drugs, hormones and vitamins have already been investigated.

The preparation of isotopically labeled drugs has to be based exclusively on the availability of radioactive starting material. The course of traditional syntheses has to be altered in virtually every case, and must be adapted to reactions yielding near-quantitative yields in each step. The high price of the decisive radioactive starting material usually makes necessary work on a small scale, and the production of 0.1 to 0.5 gram of a labeled drug represents a satisfactory achievement. Indeed, the yields are often not measured in units of weight but in millicuries of radiation emitted by the compound.

For purely scientific purposes, a drug may also be labeled with non-radioactive isotopes, and its metabolism can be followed by mass-spectrographic studies. This precludes, however, application to therapy, and requires cooperation with a physicist trained in mass-spectrographic technic, whereas any chemist or biologist can evaluate radioactivity with a Geiger counter.

Radiosodium chloride has been injected and used to delineate accurately the extent of intact circulation in gangrened legs. Radioactivity, that is, circulation of NaCl has been detected by this device in the leg below the knee even if gross examination would have indicated the necessity of amputating above the knee. The water content of the body can also be determined on the basis of radiosodium distribution.

Radiostrontium and radiocarbon compounds are deposited as carbonates in bones, teeth and sarcomas and can be used to diagnose disease of the hard tissues, or to destroy sarcomatous tissue in the body.

Sodium radioiodide is rapidly concentrated in the thyroid gland and its irradiation arrests the spread of malignant tumors in this organ. Before therapeutic doses are administered, the salt is given in smaller amounts to

determine whether the cancer tissue or its metastases will respond to radiation therapy.

In a similar manner, sodium radiophosphate is concentrated in tissues containing phospholipids, and has been found to accumulate in erythrocytes and in those body structures from which red blood cells arise (erythropoietic tissues). Administration of radioactive phosphates has led to a temporary arrest of fatal leukemia and prolongation of life by many years. This treatment has the advantage over irradiation with X-rays in that the latter strike a wide tissue area and cause radiation sickness on repeated use, while the radiation produced by radiophosphorus is localized and concentrated in the diseased tissue only.

This selective radiation makes possible treatment of small cancerous areas on the skin without risking radiation burns in the surrounding sections. Radiogold colloid can be injected directly into tumor tissue and destroys it without diffusing into the surrounding healthy tissue. The short half-life time of this particular radiation also eliminates the danger of cumulative radiation effects in the body. Similar advantages are attributed to radiocobalt salts which have found increasing use in the treatment of malignancies.[8]

Several organic compounds have been found to afford considerable prophylactic protection against lethal doses of Roentgen rays. Among them are thiourea, and *p*-aminopropiophenone.[9]

[8] "Symposium on Radioactive Isotopes," *J. Clin. Invest.*, **28,** 1375 (1949).
[9] Storer and Coon, *Proc. Soc. Exp. Biol. Med.*, **74,** 202 (1950).

CHAPTER XXVI

Thyroxine and Antithyroid Drugs

Antithyroid drugs are used to counteract the effects, or to inhibit the synthesis of the active principle of the thyroid gland. In order to appreciate their significance, a brief discussion of the gland and its hormones is necessary.

Clasping the upper end of the back of the trachea in man and mammals lies a vascular endocrine gland, the thyroid. It weighs approximately 95 grams in the human. Thyroidal tissue is found in various forms in many higher and lower animals, and seems to fulfill the mission of bringing about and accelerating maturation of the animal.[1] In addition, the gland exerts a profound influence on the maintenance of basal oxygen metabolism, normal oxidations and reductions, food intake and growth of tissues.

I. PHYSIOLOGICAL ACTIONS OF THE THYROID HORMONE

The main action of the active hormonal principle of the thyroid gland is its calorigenic activity, that is, its effect on the rate of oxidative cell metabolism. All tissues of the animal body are affected. Deficiency of thyroid hormone (hypofunction, hypothyroidism) is expressed by characteristic symptoms grouped together under the name of myxedema. The biochemical cause of these symptoms is unknown, but in hypothyroidism many other normal metabolic functions, such as salt and water balance in the tissues, the normal efficiency of the central nervous system, as well as the operation of the circulatory system are altered or impaired. Moreover, the production of thyroid hormone is stimulated by "thyrotropin", a hormone of the anterior lobe of the pituitary gland. This gland in turn is affected by hypo- of hyperthyroidism, as are other endocrine glands, the parathyroids and the sex glands (gonads). Any upset of normal thyroid function therefore sets in motion a long series of physiological events related to the activities of the affected organs.

Hypothyroidism resulting in myxedema is observed either as a disease in adults or juveniles, or as an inherited deficiency in infants and children.

[1] Means, Albert, Astwood, Chaikoff, Dempsey, De Robertis, Goldsmith, Leblond, McGinty, Rawson, Reineke, Salter, and Taurog, *Ann. N. Y. Acad. Sci.*, **50**, 279–508 (1949).

Unless corrected by early administration of daily oral doses of thyroid preparations, such children become victims of cretinism. Lack of iodine in the diet, particularly in the center of vast continents which had never been inundated by prehistoric oceans, may be a contributing factor to endemic cretinism. Its occurrence may be reduced by mandatory incorporation of about 0.00075% of inorganic iodides into table salt.[1a]

The cause of adult myxedema is unknown. The symptoms are a decrease of metabolic rate and a general impairment of all functions, expressed even externally by a sluggish appearance with characteristic physical changes. Normal functions can be restored dramatically by administration of preparations containing thyroid hormone.

Thyroid hyperfunction (hyperthyroidism) presents a greater challenge to the medicinal chemist. In this disease an overproduction of thyroid hormone takes place and results in a condition called thyrotoxicosis or toxic goiter. Depending upon the enlarged condition (hyperplasia) of the gland and upon certain clinical symptoms resulting from the disease, one usually distinguishes between two types of thyrotoxicosis, (a) exophthalmic goiter (Grave's or Basedow's disease), and (b) Plummer's disease. As might be expected, basal metabolism is elevated, and the patient presents an emotionally exicted picture opposed to that observed in myxedema. Surgical removal of the major portion of the hyperplastic gland, or X-ray treatment, have offered the greatest relief from the distressing symptoms. Since patients having a high metabolic rate cannot be operated on readily, preoperative treatment with inorganic iodides or antithyroid drugs serves as a means of preparation for surgery.

Adjunct drugs designed to relieve irritability of patients facing thyroidectomy are sedatives, and sometimes quinidine to counteract cardiac fibrillation accompanying thyrotoxicosis.

II. THE NATURE OF THE THYROID HORMONE

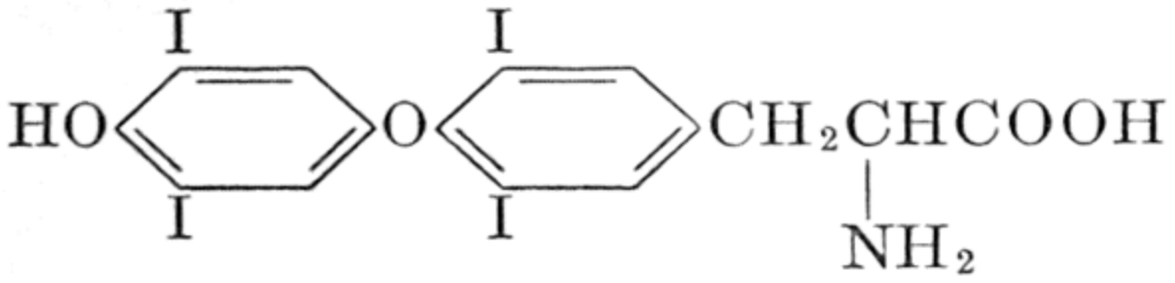
Analysis of dried or fresh thyroid glands has demonstrated that the gland contains a large amount of iodine, principally in organic linkage, plus a small percentage of iodide ion. The amounts of organic and inorganic iodine derivatives found in other tissues, and in the circulatory fluids, are insignificant in comparison with those found in the thyroid.

The fate of ingested or parenterally administered iodine compounds can be studied readily by tagging I^{127} with the radioisotope I^{131} which has a half-life of eight days. It is available from deuteron bombardment of tellurium in the cyclotron or from nuclear fission of U^{235}. As early as

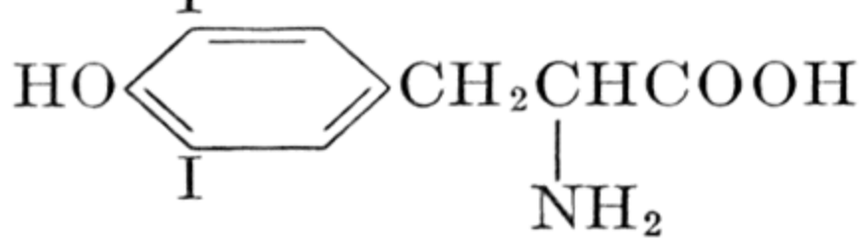
[1a] The dispensation of iodides in foods was recommended in France in 1873, based on the work of Chatin. Cf. Greenwald, *Science*, **111**, 501 (1950).

fifteen minutes after the injection of a dose of tracer potassium radioiodide into rats, a large percentage of it is concentrated in the gland, and 95% is incorporated into organic compounds.

These organic compounds of iodine comprise proteinoid materials, from which, by hydrolysis, two aromatic compounds can be isolated, namely, thyroxine (β-(3,5,3′,5′-tetraiodo-4′-hydroxydiphenyl ether)-α-aminopropionic acid, XXVI-1) and 3,5-diiodotyrosine (XXVI-2). Thy-



(XXVI-1)

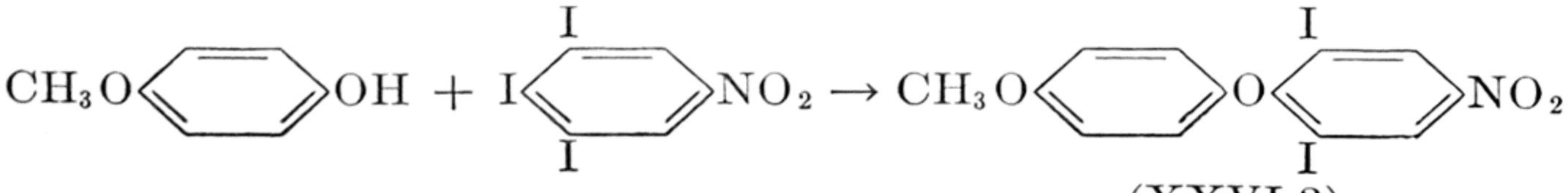


(XXVI-2)

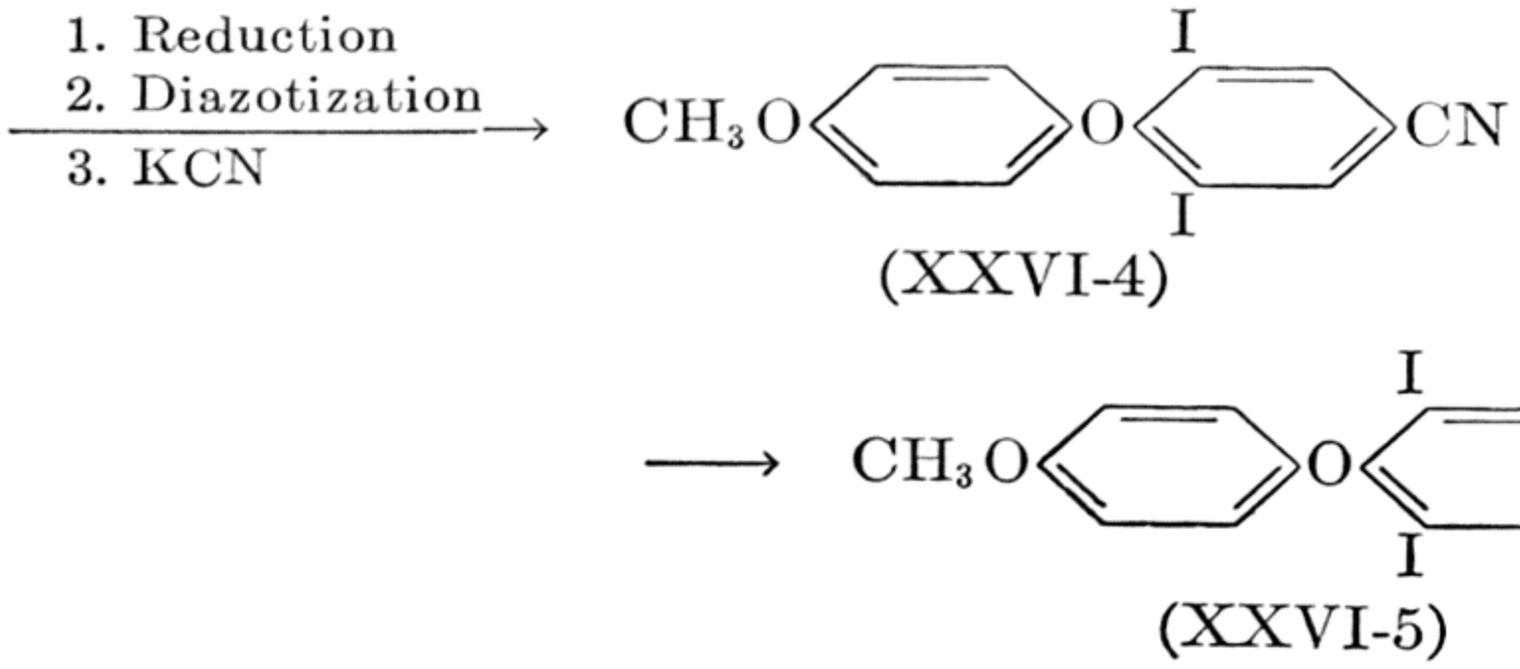
roxine is regarded as the circulating hormone of the thyroid gland,[2] although the protein thyroglobulin (molecular weight, 675,000) from which thyroxine is obtained, had previously been regarded as the carrier of hormonal activity. The major iodine-containing component of plasma has been identified as thyroxine.[2]

The structure of thyroxine was elucidated largely by Kendall,[3] and by Harington and Barger.[4] The classical synthesis by the latter investigators confirmed the structure and opened up the path to further study of the relations of well-defined products of the gland.

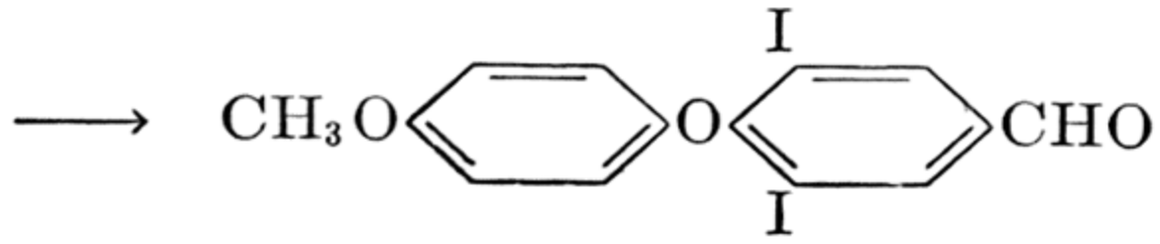
The synthesis of thyroxine started with hydroquinone monomethyl ether which was condensed with 3,4,5-triiodonitrobenzene in butanone



(XXVI-3)



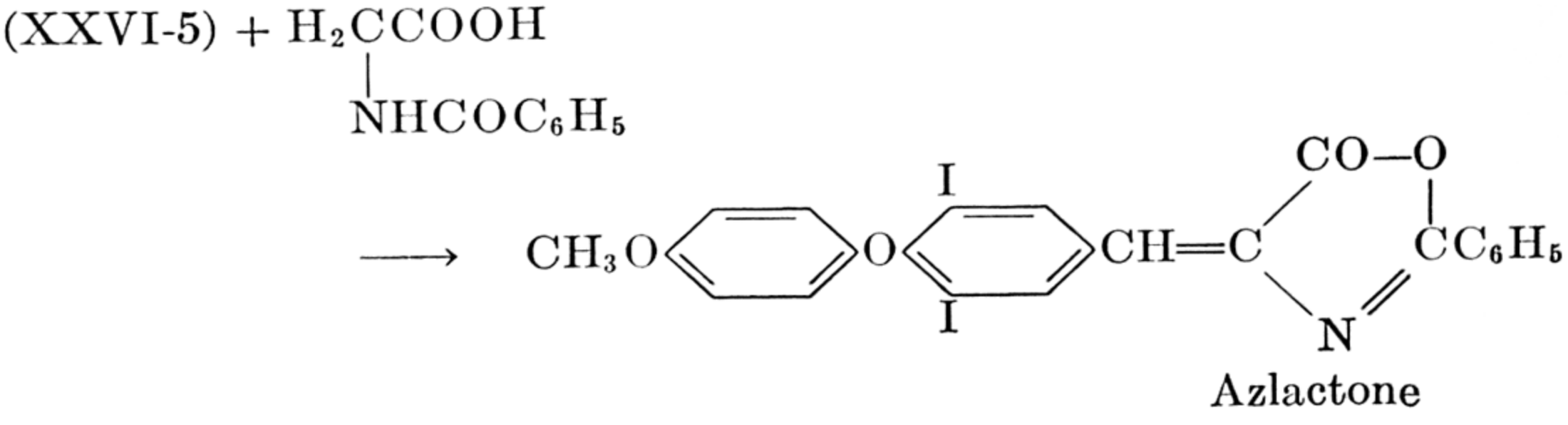
(XXVI-4)



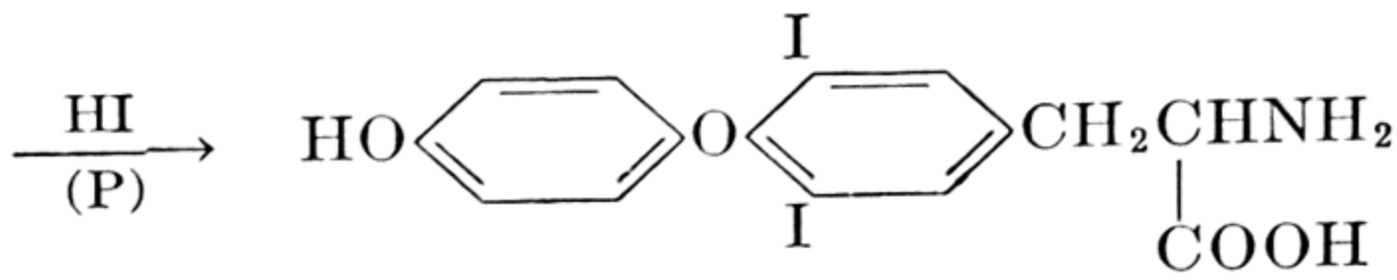
(XXVI-5)

[2] Taurog and Chaikoff, *J. Biol. Chem.*, **171,** 439 (1947); **184,** 99 (1950).
[3] Kendall, *J. Am. Med. Assoc.*, **64,** 2042 (1915); *J. Biol. Chem.*, **39,** 125 (1919).
[4] Harington and Barger, *Biochem. J.*, **21,** 69 (1927).

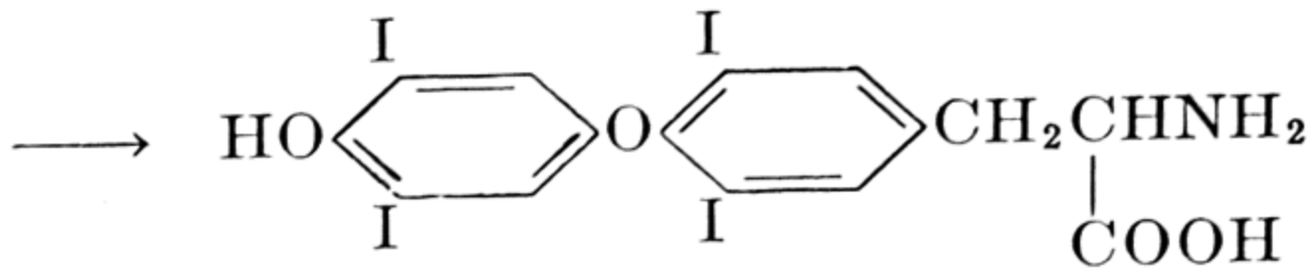
solution under the influence of dry potassium carbonate. 3,5-Diiodo-4-(4′-methoxyphenoxy) nitrobenzene (XXVI-3) thus obtained was reduced to the corresponding amine which was converted to the nitrile (XXVI-4) by a Sandmeyer reaction in anhydrous medium. The nitrile was subjected to a Stephen reduction in chloroform solution to yield 3,5-diiodo-4-(4′-methoxyphenoxy) benzaldehyde (XXVI-5). The aldehyde (XXVI-5) served as starting material for an azlactone synthesis of the alanine side chain, using hippuric acid. The unsaturated ester (XXVI-6) was reduced



(XXVI-6)



(XXVI-7)



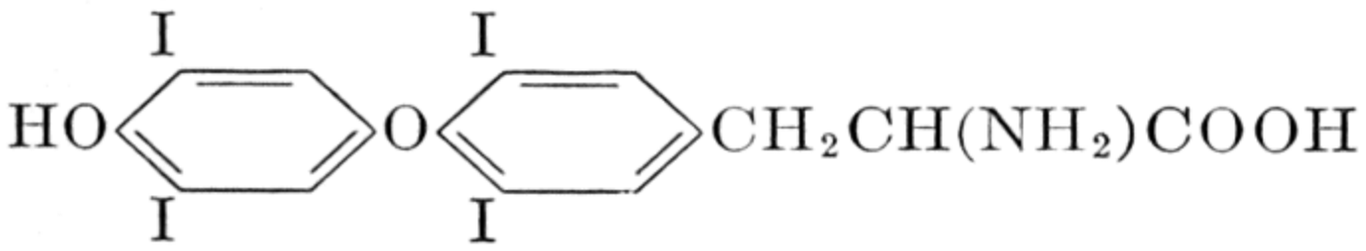
(XXVI-1)

with hydriodic acid and red phosphorus, and the β-[3,5-diiodo-4-(4′-hydroxyphenoxy)-phenyl]-α-amino propionic acid (XXVI-7) from the reduction was iodinated in ammoniacal medium. The resulting tetraiodo compound (XXVI-1) was identical with DL-thyroxine obtained from thyroglobulin by alkaline hydrolysis. Acid hydrolysis of the iodine-containing hormonal protein of the thyroid renders L-thyroxine which is in some respects no more active than the racemic mixture but shows twice the activity of the latter in some testing methods.

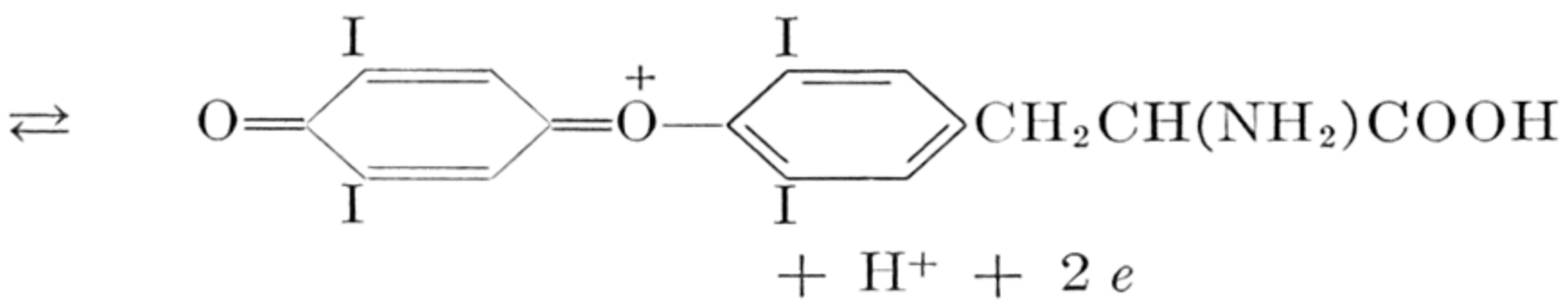
III. THE MECHANISM OF ACTION OF THYROXINE

Nieman[5] made the assumption that thyroxine exerts its hormonal activity by participating in one of the many oxidation-reduction chains in the animal organism. The linkage of thyroxine to the large protein carrier in thyroglobulin, and the profound influence of the hormone on oxygen metabolism lends credence to this hypothesis.

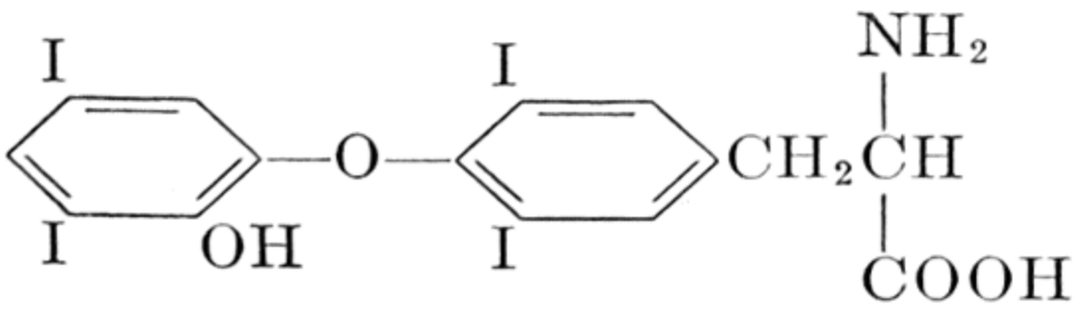
As an explanation of thyroxine activity, the following equation can be set up:



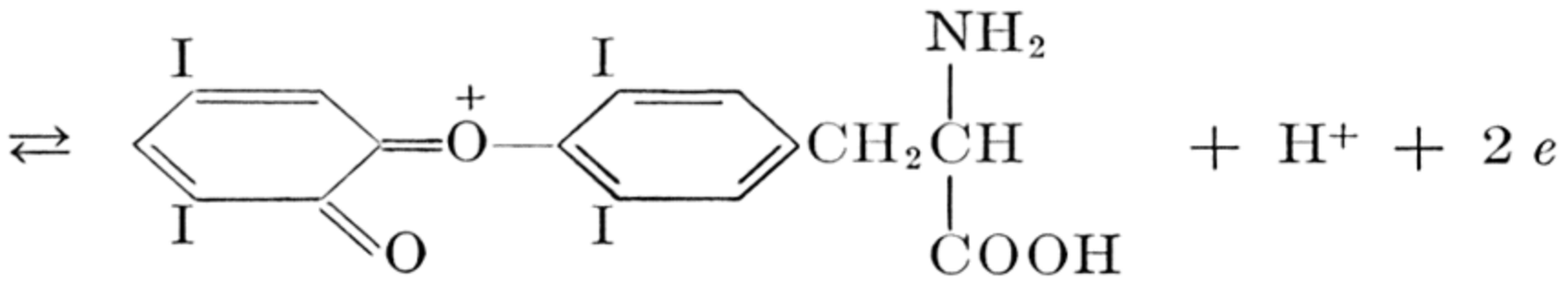
(XXVI-1)



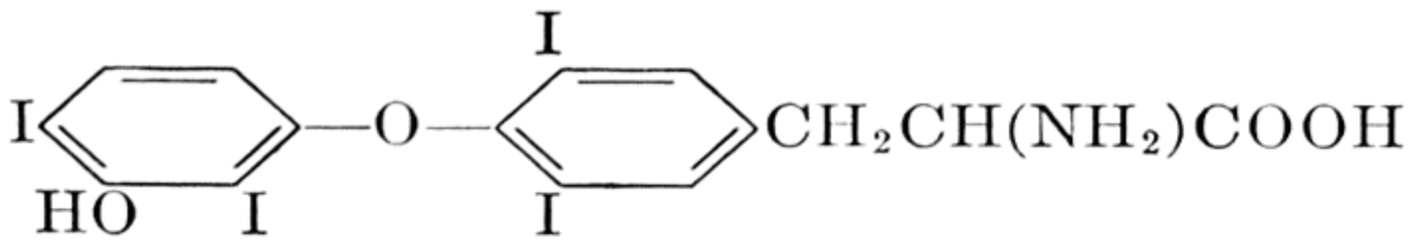
Only compounds having a potential quinonoid arrangement of their aromatic oxygen functions should therefore be capable of thyroxine activity. This hypothesis was verified by testing two isomers, (XXVI-8) and (XXVI-9).



(XXVI-8)



(XXVI-10)



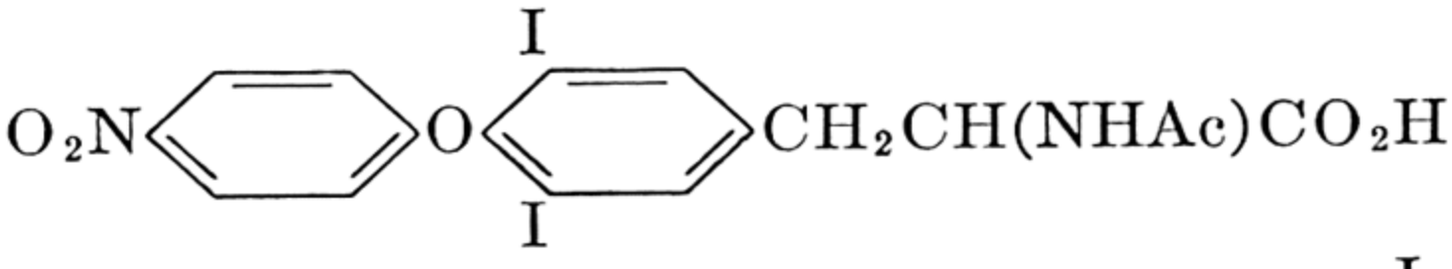
(XXVI-9)

[5] Nieman and Redeman, *J. Am. Chem. Soc.*, **63,** 1549 (1941). Nieman and Mead, *ibid.*, **63,** 2685 (1941).

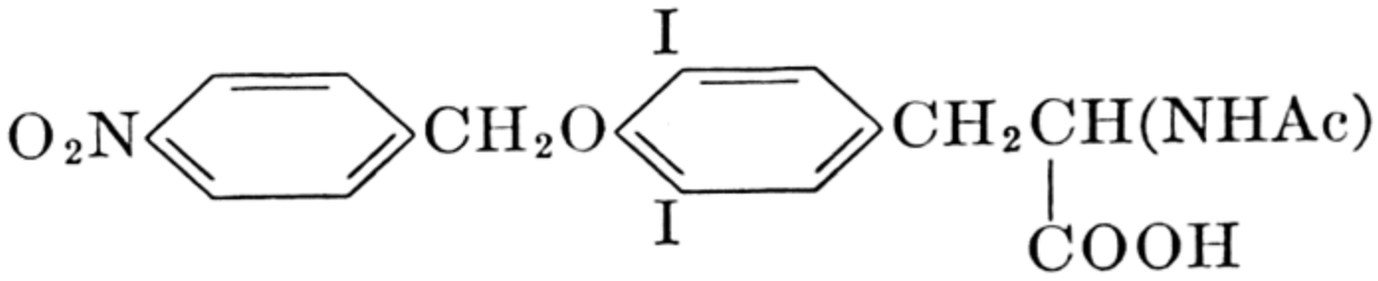
Only the *o*-hydroxy isomer (XXVI-8) can be oxidized to a quinonoid form (XXVI-10); it exhibits thyroxine activity, but because of its lower oxidation potential, only 1/25th that of natural thyroxine. The *m*-hydroxy derivative (XXVI-9) is incapable of quinone formation, and has been found inactive.

IV. METABOLITE ANTAGONISTS OF THYROXINE

Based on the fact that structurally similar compounds may either simulate each other's actions, or interfere with each other's biological reactions, Woolley[6] prepared the *p*-nitrophenyl (XXVI-11) and *p*-nitrobenzyl (XXVI-12) ethers of N-acetyldiiodotyrosine, and tested them for a possible conversion to thyroxine-like compounds. Both these derivatives exhibited



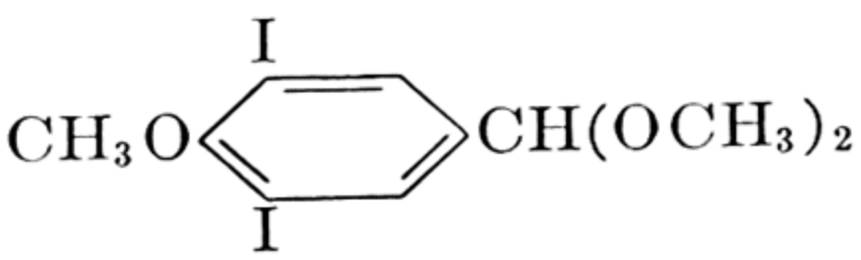
(XXV-11)



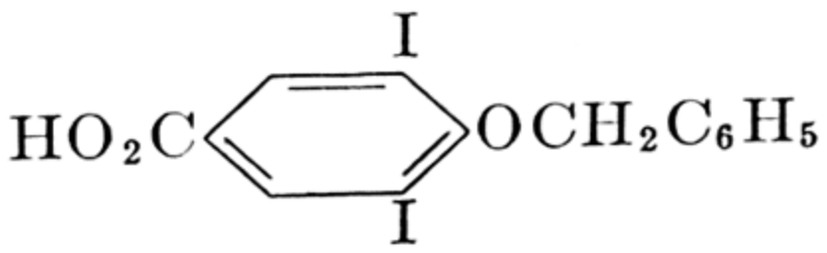
(XXVI-12)

antithyroxine properties in tadpoles and in mice but also evoked certain effects of the hormone. The corresponding benzyl and butyl ethers were inactive, but the carboxybenzyl ether exhibited activity.[6a]

Even structurally simpler iodinated compounds can reduce oxygen consumption after an increase produced by administration of thyroxine. 3,5-Diiodoanisaldehyde dimethylacetal (XXVI-13) and 3,5-diiodo-4-benzyloxybenzoic acid (XXVI-14) possess this property.[7]



(XXVI-13)



(XXVI-14)

Among other compounds which can overcome effects of thyroxine are certain iodinated phenoxyacetic acids, 4-hydroxy- and 4-benzyloxy-3,5-diiodobenzoic acids, N-(4′-hydroxy-3′,5′-diiodobenzoyl)-3,5-diiodotyrosine, and 2-dimethylaminomethyldibenzofuran.[7a]

[6] Woolley, *J. Biol. Chem.*, **164,** 11 (1946).
[6a] Winzler, quoted by Holland, *Am. J. Pharm.*, **121,** 441 (1949).
[7] Editorial, *Nature*, **164,** 699 (1949).
[7a] Barker, Dirks, Klitgaard, Wawzonek and Wang, *Federation Proc.*, **9,** 8 (1950).

V. THE BIOLOGICAL SYNTHESIS OF THYROXINE

During their work on the laboratory synthesis of thyroxine, Harington and Barger suggested the possibility that the gland may make this hormone from its ever-present companion in the thyroid, 3,5-diiodotyrosine. This hypothesis is supported by an *in vitro* experiment. When 3,5-diiodotyrosine is incubated at 60° in slightly alkaline medium, preferably with vigorous stirring and aeration, as much as 2.8% of the theoretically possible yield of thyroxine is obtained after 18 to 20 hours. The reaction appears to be catalyzed by manganese tetroxide.[8] It will be seen that the assumption of an analogous synthesis of the hormone *in vivo* has had a profound bearing on the explanation of the mechanism of action of antithyroid substances. The sequence of reactions involved must therefore be studied more closely.

Based on the findings in the oxidation of *p*-cresol,[9] the conversion of diiodotyrosine to thyroxine can be pictured[10] first as an oxidative coupling of two molecules of diiodotyrosine (XXVI-15) to an intermediate (XXVI-16), which could suffer dissociation with the loss of one alanine side chain and formation of thyroxine (XXVI-1) and iminopyruvic acid (XXVI-17). The latter is then hydrolyzed to pyruvic acid and ammonia and these two products have actually been identified in the reaction mixture.

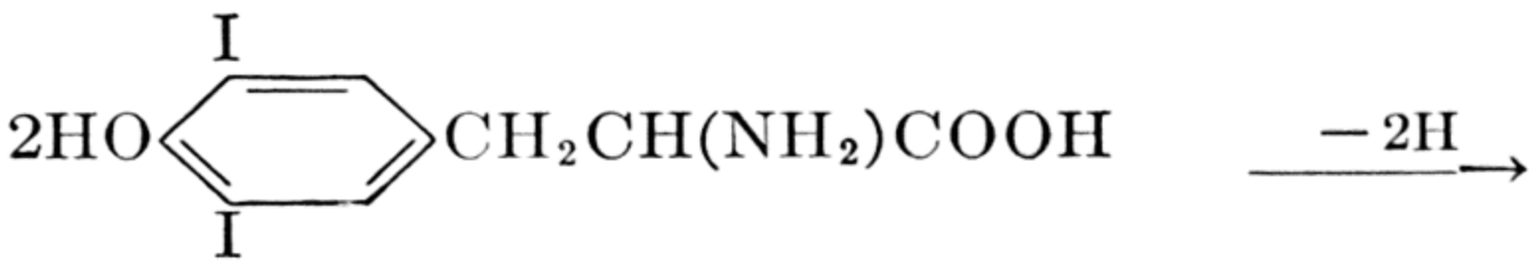
An interesting light is thrown on the biosynthesis of thyroxine by the ease with which it can be obtained by iodination of various proteins. Casein, for instance, can be converted to an iodinated high-molecular product which shows distinct thyroidal activity. Under controlled conditions, many proteins can be iodinated to materials from which crystalline DL-thyroxine can be elaborated after hydrolysis with barium hydroxide solution. Hydrolysis with butanolic sulfuric acid helps to avoid racemization and leads to pure L-thyroxine.[11] There is no indication that free tyrosine is present in proteins, but we must assume that this amino acid is linked in the protein molecule by the typical peptide bond (XXVI-18). Since the thyroxine formed in the iodination of proteins is isolated only after rather strenuous hydrolysis, it too must be part of a polypeptide structure. The conclusion is therefore inevitable that not free tyrosine, but the tyrosyl group on a protein level is iodinated to a diiodotyrosyl

[8] Reineke, *Ann. N. Y. Acad. Sci.*, **50,** 450 (1949).

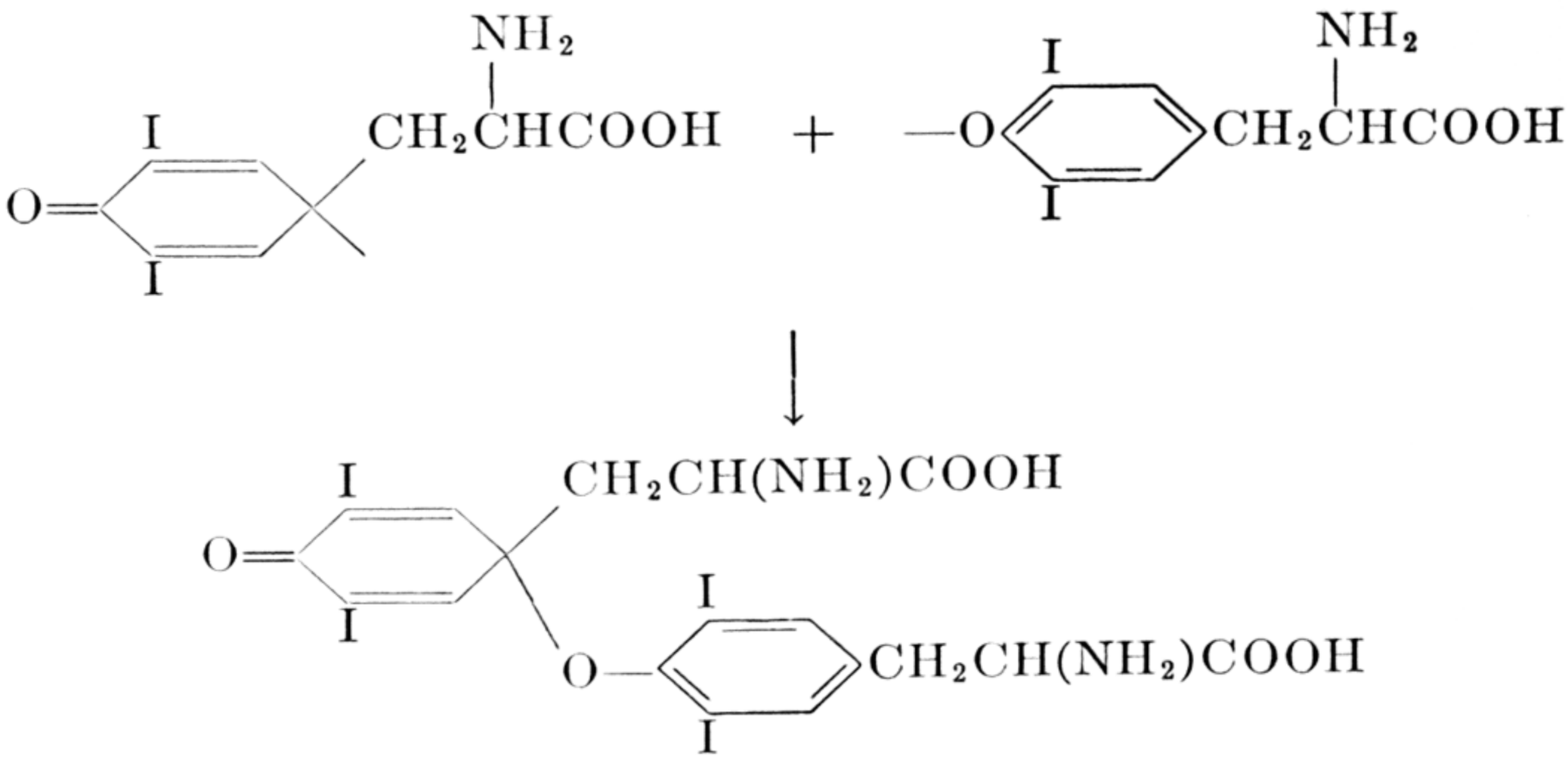
[9] Pummerer, Putfarchen, and Schopflocher, *Ber.*, **58,** 1808 (1925). Harington, *J. Chem. Soc.*, **193,** (1944).

[10] Johnson and Tewkesbury, *Proc. Natl. Acad. Sci.*, **28,** 73 (1942).

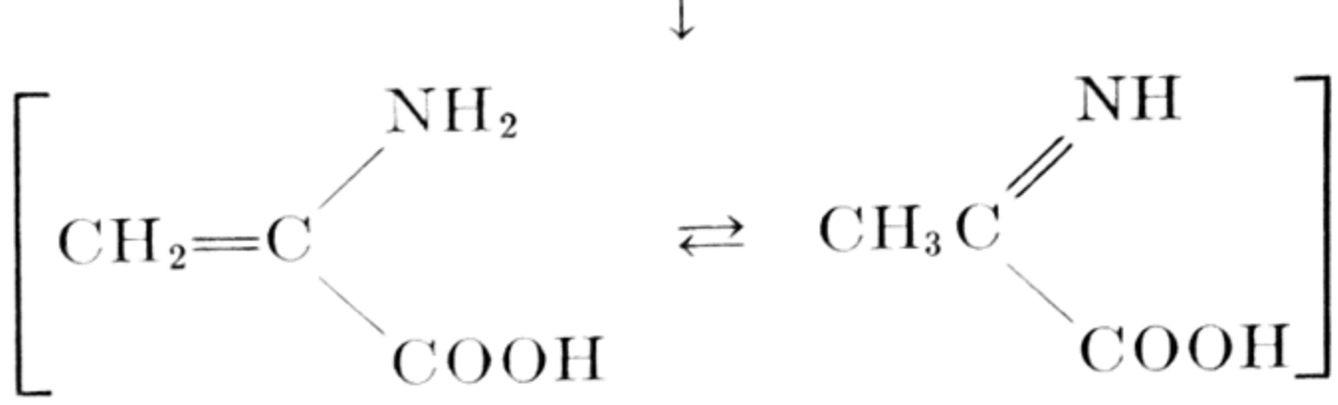
[11] Ludwig and Mutzenbecher, *Z. physiol. Chem.*, **258,** 195 (1939). Harington and Rivers, *Nature*, **144,** 205 (1939). Foster, Palmer, and Leland, *J. Biol. Chem.*, **115,** 467 (1936).



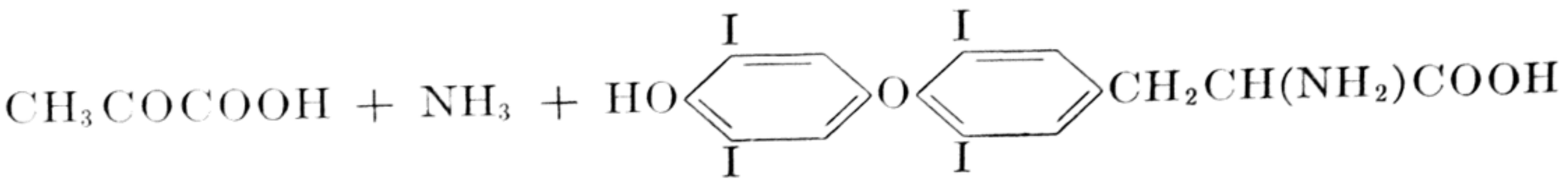
(XXVI-15)



(XXVI-16)

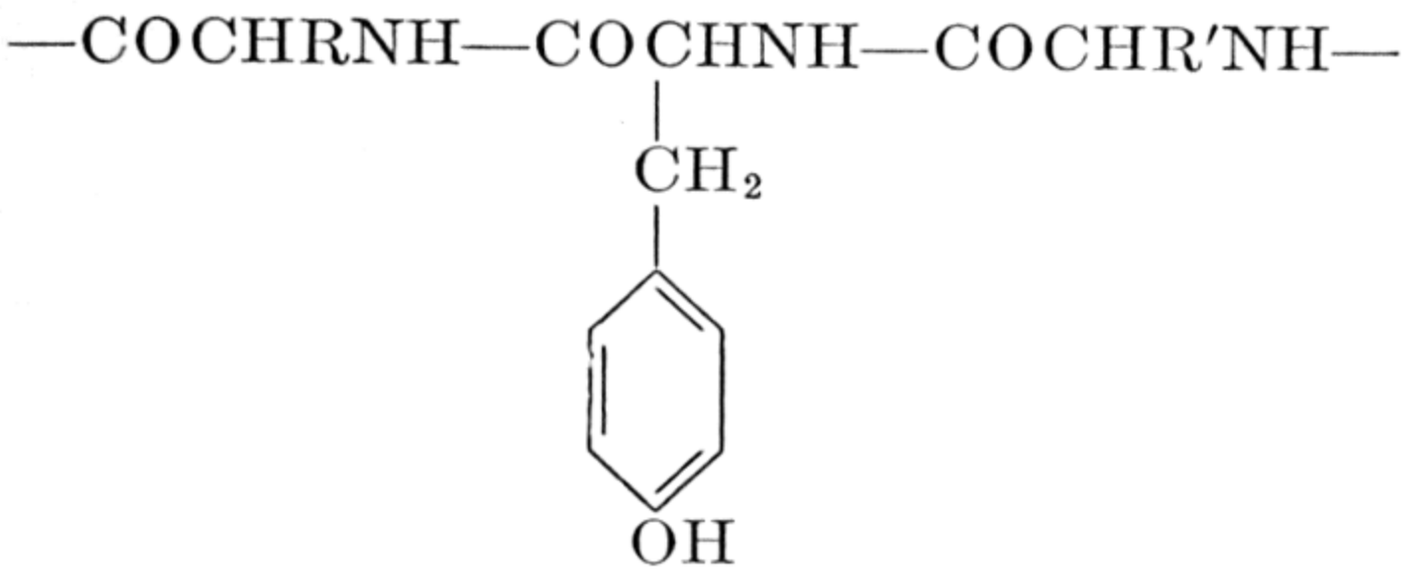


(XXVI-17)

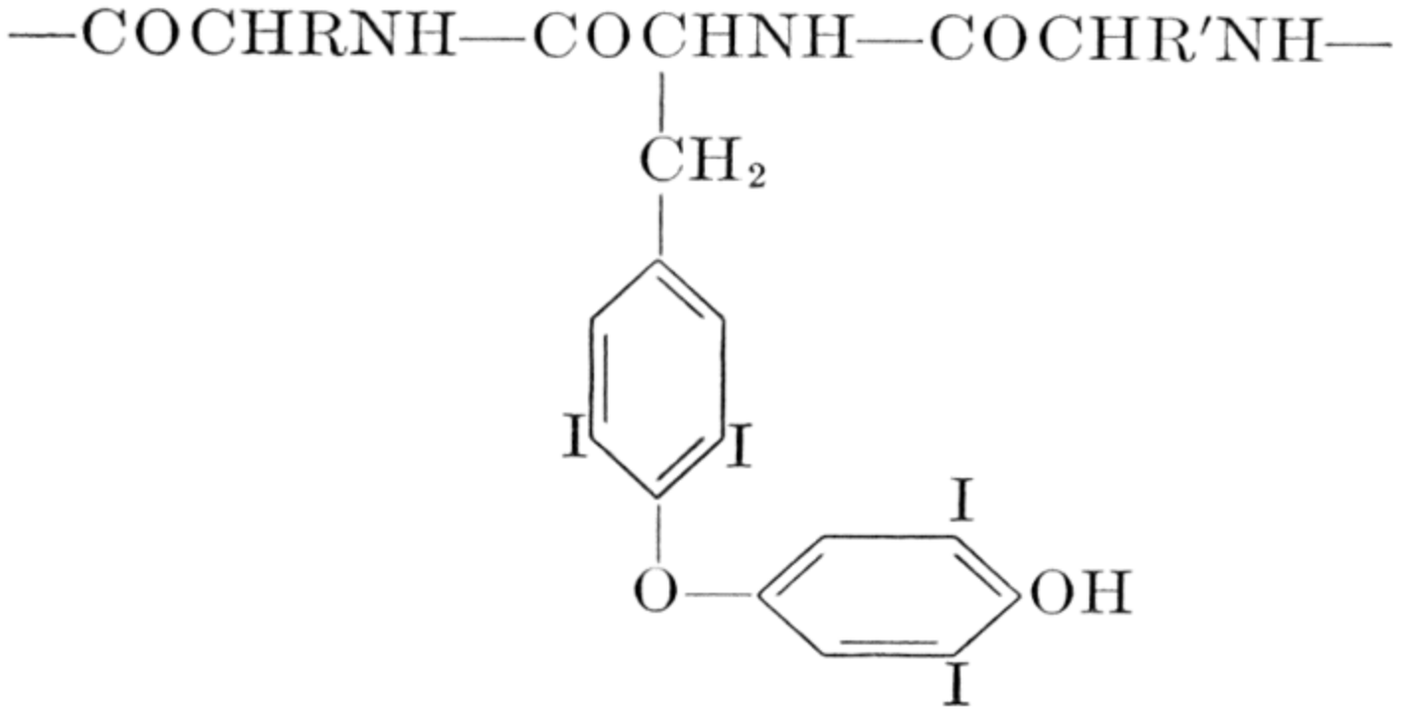


(XXVI-1)

group on the same level, and that thyroxine is formed *within the protein molecule* by the oxidative coupling of two such radicals and the subsequent splitting-off of one side chain (XXVI-19). The reaction proceeds without the aid of enzymes, and it may be assumed that this holds for the parallel synthesis of thyroxyl from diiodotyrosyl groups in the thyroid gland.



(XXVI-18)



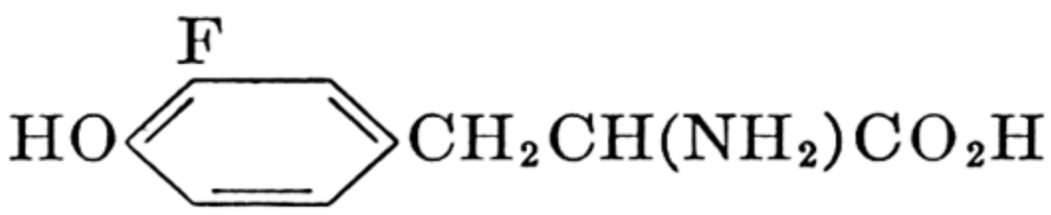
(XXVI-19)

None of the proposed mechanisms of thyroxine formation *in vivo* accounts for the iodination of tyrosine in a satisfactory manner. The conversion of iodide ion into organically covalent-bound iodine must involve removal of the electron of the ion. The iodide ion thus becomes iodine, atomic or molecular, and this is immediately used up in the iodination of tyrosine. No biochemist will be satisfied with the idea that free iodine could exist for even an instance in the thyroid cell, or that it would react with water to form hypoiodic acid, HIO, which would act as the iodinating agent. Nevertheless, tyrosine *is* iodinated, and the necessary iodine arises by an oxidative step from iodide ion. Whether the oxidation is carried out by oxygen itself, or by hydrogen peroxide, or by hydrogen peroxide under the influence of peroxidase, is unknown. No other known tissue enzyme could be the catalyst for this oxidation because of the high potential of the reaction.

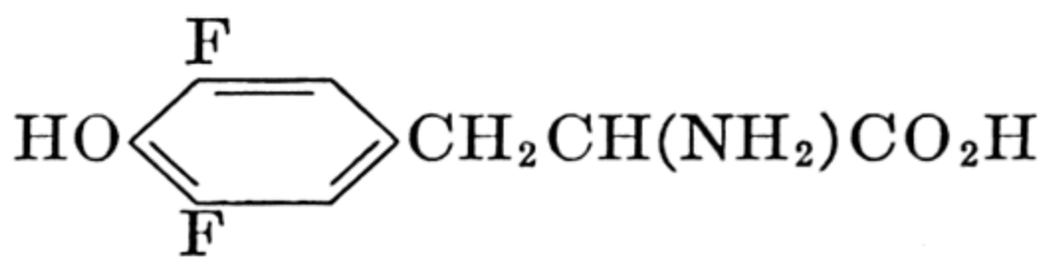
If the overproduction of the thyroid hormone is to be counteracted by drugs, the synthesis of thyroxine or thyroglobulin might be blocked at any of the synthetic steps. The oxidation of iodide ion to iodine might be prevented by a specific antioxidant, or the iodine might be absorbed competitively by a compound which reacts faster than tyrosine. Or else, blocking of any enzyme system which may catalyze the oxidative coupling of the two diiodotyrosyl groups would prevent formation of the hormone.

The alternative biochemical mechanism for the prevention of hyperthyroidism would be an interference with the effects of the hormone of the gland. This might be achieved by special compounds isosteric with thyroxine or in some other way capable of taking its place in the reactions with chemicals of the effector organs. With this in mind, the role of iodine for thyroid hormone activity has been tested.

It is less certain today than it had been several years ago whether iodine is the only halogen that produces thyroxine activity in analogs of the hormone. Several compounds containing chlorine and bromine in place of iodine have been tested with negative results. However, 3-fluoro- (XXVI-20) and 3,5-difluorotyrosine (XXVI-21) possess some thyroxine-like as well as thyroxine-antagonist properties.[12]

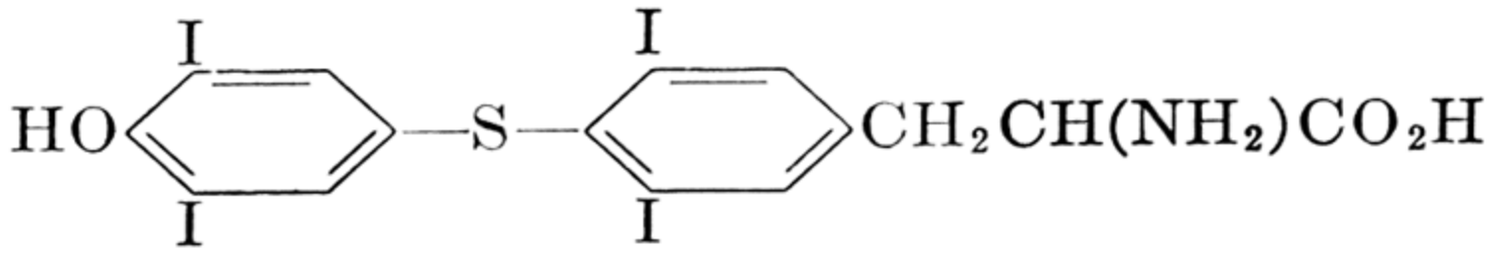


(XXVI-20)



(XXVI-21)

In order to test the possibility of controlling the output of the thyrotropic hormone from the anterior pituitary gland, Harington[13] prepared the the thioether analog of thyroxine (XXVI-22). This compound accelerated the metamorphosis of tadpoles at a rate about one fifth of that of thyroxine, and was thus analogous rather than antagonistic to the hormone.



(XXVI-22)

VI. IODIDES IN THYROID THERAPY

The beneficial action of iodides in some forms of myxedema is understandable if the condition is caused by a lack of iodine in the diet. In dietary iodine deficiency, the amount of "colloid" of the gland, that is the material in which iodine is utilized for the synthesis of the hormone, decreases, while the gland becomes enlarged and hypertrophied and works at maximum capacity, in order to make up for the lack of the essential element. The enlarged gland is called simple or hyperplastic goiter; administration of iodides may gradually return the gland to normal, unless the

[12] cf. English, Mead, and Nieman, *J. Am. Chem. Soc.*, **62,** 350 (1940).
[13] Harington, *Biochem. J.*, **43,** 434 (1948).

goiter has reached a very advanced stage. In a sense, iodine exerts here an antithyroid effect by decreasing the size of the gland markedly, but of course thyroid hormone synthesis is promoted.

The effect of iodides in toxic goiter has not yet been explained. There is no doubt that, contrary to all obvious theoretical expectation, the condition is benefited temporarily by administration of iodides. One of the most favored explanations of this fact is the decrease in thyroxine-promoting pituitary hormone under the influence of iodides. An able discussion of these hypotheses has been presented by Astwood.[14]

The fate of administered iodides has been clarified by studying the rate of conversion of these halide ions to protein-bound iodine. The gland has no ability to store large amounts of inorganic iodides under normal conditions but uses the ions soon for the iodination process. If, however, the normal store of thyroxine of the gland has been decimated by an effective antithyroid agent (thiouracil), and a dose of sodium iodide is then administered, the organ rapidly concentrates relatively enormous quantities of inorganic iodide by withholding it from the circulation.

The remarkable ability of the thyroid gland to concentrate iodides is inhibited by the thiocyanate ion (SCN^-). This ion, a pseudo-halide, is widely distributed in blood and saliva and probably arises from the detoxication of cyanides. It may also be formed from vegetable constituents of the diet which contain substances that can be converted to thiocyanates by the animal organism. Among such substances are the mustard oils, RNCS, many nitriles and cyanohydrins. If they are regular dietary factors, the thyroid gland might be constantly inhibited in its iodide uptake, even though an adequate supply of the latter ion is present in the food. Thus, the long-known phenomenon may find an explanation that both goiter and myxedema (iodine deficiency) may be caused by very small amounts of sodium thiocyanate.

Inorganic thiocyanates cannot be used clinically because of this very drawback: they inhibit formation of the hormone, to be sure, but also deplete the gland of its iodine store to such an extent that hyperthyroidism is followed by severe hypothyroidism.

Of organic nitriles, acetonitrile[15] has received most attention because of its relatively low toxicity. Acetonitrile produces goiters which can be prevented by administration of iodides. An explanation of the action of acetonitrile may be its adverse effect on oxygen consumption. There is then an increased demand upon the gland to overcome this inhibition, and hyperplasia results.

[14] Astwood, *Ann. N.Y. Acad. Sci.*, **50,** 419 (1949).
[15] Marine, Baumann, Spence, and Cipra, *Proc. Soc. Exptl. Biol. Med.*, **29,** 772 (1932).

VII. EXPERIMENTAL EVALUATION OF ANTITHYROID ACTIVITY

The principle of the testing methods in mammals is essentially the determination of the relative effectiveness of the materials in inhibiting thyroid hormone production. The gland of the common test animal, the rat, undergoes enlargement (hyperplasia) and the amount of hyperplasia is studied microscopically. Maximal enlargement and proliferation of acinar cells, and complete loss of colloid are a measure of greatest activity.[16]

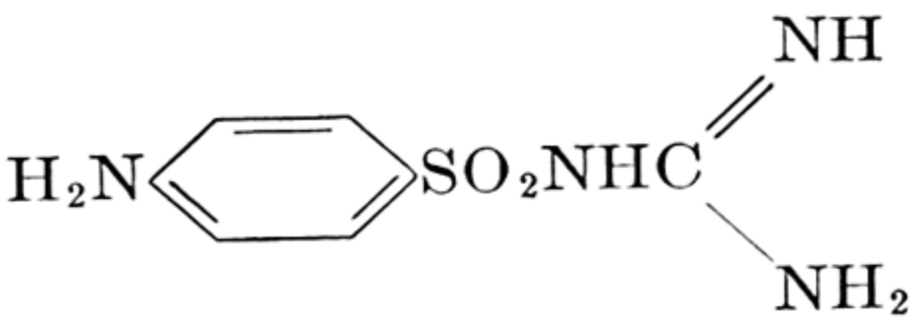
Another test, used less widely, consists of suspending tadpoles in a solution of the test substance, and observing the rate of development of the animals. The inhibition of the rate of dehydrogenase-catalyzed oxidations in the presence of thyroxine, as produced by the test substance, has been proposed as an *in vitro* method.

Two other test methods have been described recently. One is based on the decreased resistance of mice to lack of oxygen, the other one on the acute weight loss in rats receiving thyroxine.[17]

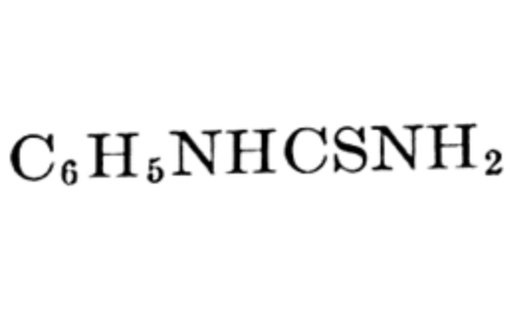
The degree of hyperplasia produced by a given material is spoken of as its goitrogenic activity. Many investigators have chosen thiouracil as reference material (antithyroid activity = 1). As with all other drugs, the medicinal usefulness of a goitrogenic compound depends on its therapeutic index.

VIII. INHIBITORS OF THYROXINE SYNTHESIS

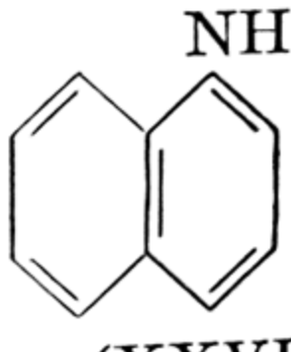
Two accidental observations made in the course of charting the chronic toxicity of unrelated drugs layed the foundation of modern antithyroid research. The first of these chance discoveries occurred when it was found that prolonged feeding of sulfaguanidine (XXVI-23) to rats produced marked thyroid hyperplasia.[18] Similar observations have since been made with other sulfonamides and with aromatic sulfones, and the goitrogenic properties of the latter have contributed much to discrediting some of them as useful chemotherapeutic agents.



(XXVI-23)



(XXVI-24)



(XXVI-25)

[16] McGinty and Bywater, *J. Pharmacol. Exptl. Therap.*, **85,** 129 (1945). Astwood, *ibid.*, **78,** 80 (1943).

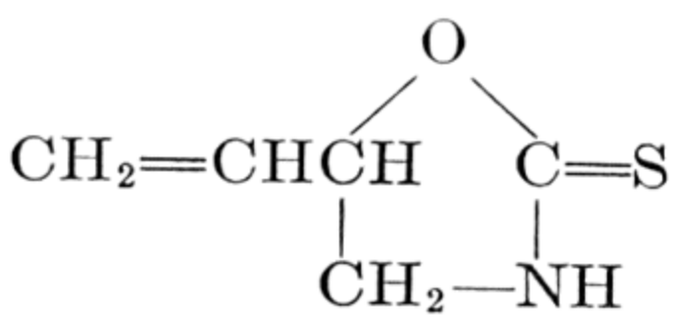
[17] Hutcheon, *ibid.*, **94,** 308 (1948).

[18] MacKenzie, MacKenzie, and McCollum, *Science*, **94,** 518 (1941).

The second fact concerned goitrogenic properties of aromatic thioureas. Both phenylthiourea (XXVI-24) and α-naphthylthiourea (ANT) (XXVI-25) show remarkable and selective toxic effects in rodents; ANT has been used widely to exterminate rats because of their role as hosts to disease-carrying insects. During some work concerning the mechanism of their toxic activity, the ability of these agents to produce thyroid hyperplasia was encountered.[19]

The thioureas contain the group $>$ N—CS—N $<$ as the structural unit which could cause their toxic and goitrogenic behavior. It had been known that a diet of cabbage or other vegetables of the Brassica family could produce thyroidal enlargement in rabbits. The natural occurrence of mustard oils (RNC═S) in plants suggested that the active principle of Brassica seed might be a compound containing the group N—C═S, perhaps a derivative of thiourea. Allylthiourea was tested on the basis of this prediction, and proved to be strongly goitrogenic.[20]

The goitrogenic antithyroid factor of the yellow turnip (rutabaga) has now been recognized as (−)-5-vinyl-2-thioxazolidone (XXVI-26). It has also been found in cabbage, kale and rape. The compound is equal in activity to 6-*n*-propylthiouracil in man (see below), and acts by preventing thyroxine synthesis as shown by experiments with radioiodine.[21]



(XXVI-26)

Thiourea (H_2NCSNH_2) itself has similar properties.[22] Its toxicity was low enough to warrant clinical experimentation. Thiourea was the first drug to be used in human thyrotoxicosis before thiouracil became available. The common daily dose of thiourea is 1–3 grams.[23]

Most of the derivatives of thiourea which do not contain the group ═N—CS—N═ in a ring are more toxic than thiourea, and only few of the many derivatives tested have been found more active than the parent compound. Tetramethylthiourea, $[(CH_3)_2N]_2CS$, and sym. diethylthiourea, $(C_2H_5NH)_2CS$, were as much as three times as active as thiourea, but

[19] Richter and Clisby, *Proc. Soc. Exptl. Biol. Med.*, **48,** 684 (1941); *Arch. Path.*, **33,** 46 (1942).

[20] Kenedy, *Nature*, **150,** 233 (1942).

[21] Astwood, Greer, and Ettlinger, *Science*, **109,** 631 (1949). Astwood, *Ann. Intern. Med.*, **30,** 1087 (1949).

[22] Astwood, Sullivan, Bissell, and Tyslovitz, *Endocrinology*, **32,** 210 (1943).

[23] Astwood, *J. Am. Med. Assoc.*, **122,** 78 (1943).

increased toxicity cancelled out this advantage. Allylthiourea has been tested clinically, and so have a few other alkylated, acylated, and aryl derivatives. None of these compounds have become useful drugs.

Incorporation of the thiourenyl group into a heterocyclic ring has led to some of the most active antithyroid drugs now known. A large variety of ring systems can be thought to be derived from thiourea, and compounds in almost every one of these series have been prepared and tested.

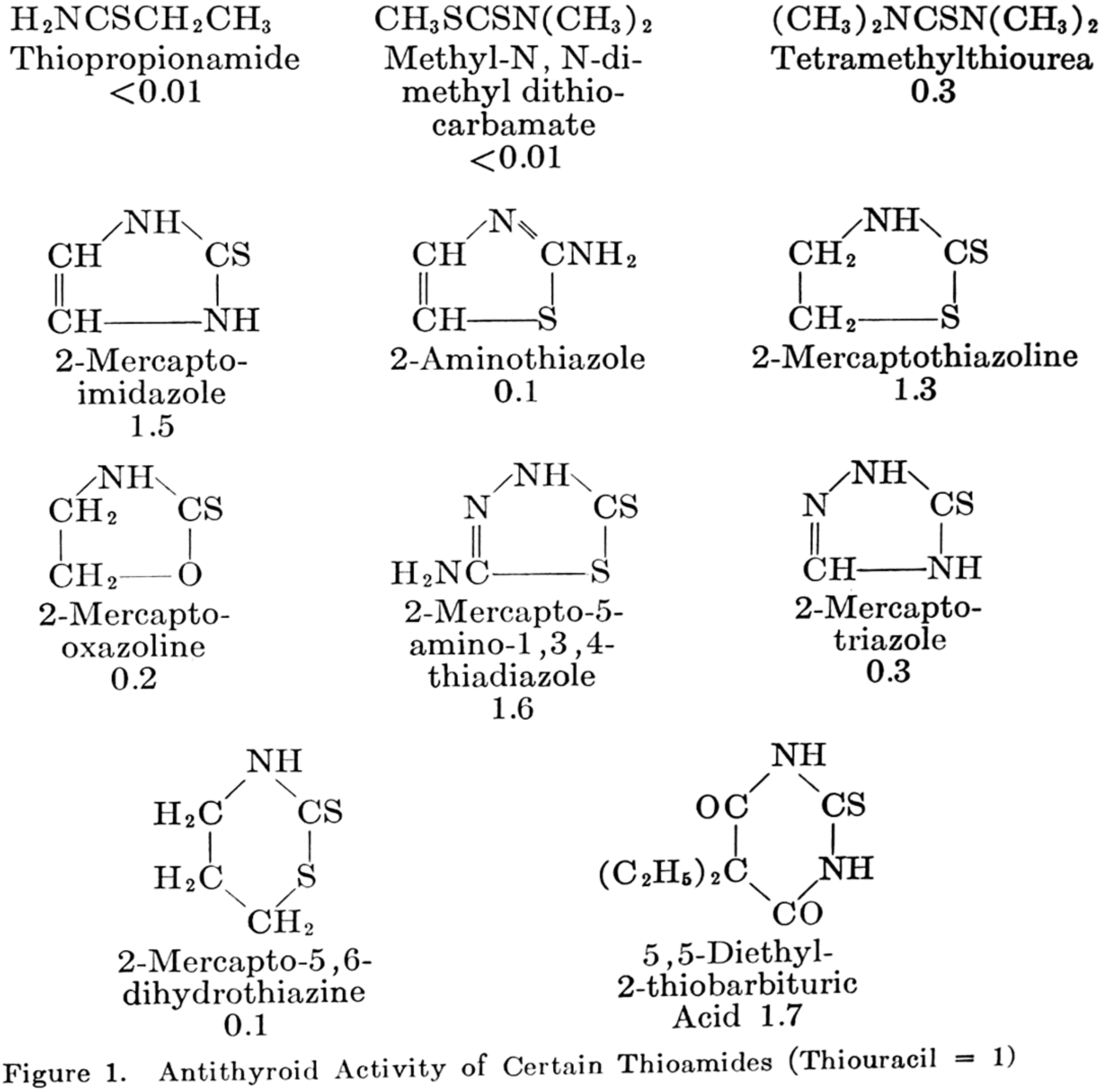
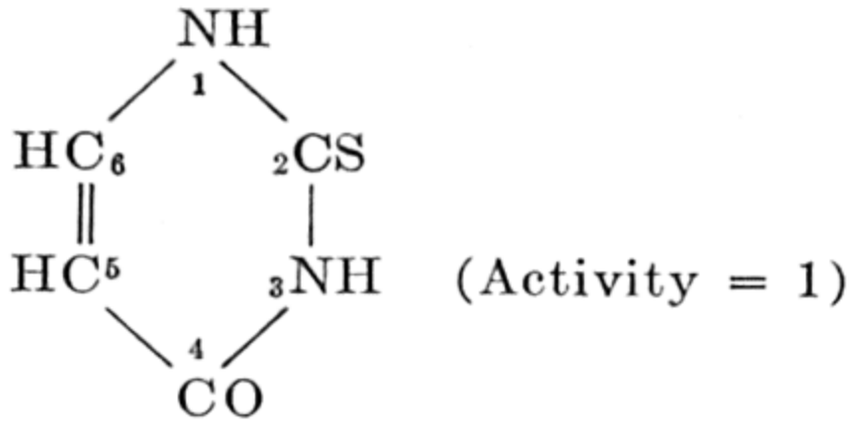


Figure 1. Antithyroid Activity of Certain Thioamides (Thiouracil = 1)

In Figure 1 are tabulated compounds representative of some cyclic thioureides as well as analogous ring systems in which urea nitrogen atoms have been replaced by oxygen or sulfur. Some open-chain analogs of thioureas have been included for further comparison. The antithyroid activ-

ity is listed below the names of the compounds, 2-thiouracil with activity = 1 serving as a standard.

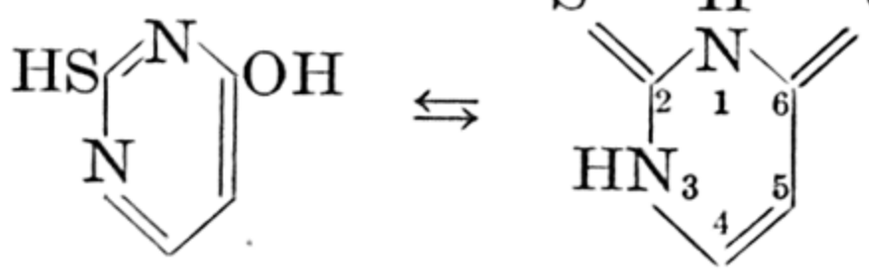
TABLE I. ANTITHYROID ACTIVITY OF DERIVATIVES OF 2-THIOURACIL[24]



(Activity = 1)

Position	of R	Activity
6	CH_3	1
6	C_2H_5	10
6	n-Pr	11
6	iso-Pr	9
6	$(CH_3)_2CHCH_2$	5
6	n-C_4H_9	6
6	$(CH_3)_3C$	9
6	n-C_5H_{11}	1.3
6	cyclo-C_6H_{11}	1.2
6	C_6H_5	1.0
6	$C_6H_5CH_2$	10.0
6	$C_6H_5CH_2CH_2$	1.2
5, 6	$(CH_3)_2$	1.2
5, 6	$(CH_3),(C_2H_5)$	3.5
5, 6	$(C_2H_5),(CH_3)$	0.9
5, 6	$(C_2H_5)_2$	2.0
6	$C_6H_{11}CH_2$	10.0
2, 5	$(CH_3),(Cl)$	1.3
2, 5	$(CH_3),(Br)$	1
5	I	1

2-Thiouracil (XXVI-27) and several of its alkyl substituted derivatives have been studied extensively as antithyroid agents. 2-Thiouracil



(XXVI-27)

has been used successfully in patients showing hyperplasia and increased hormonal activity of the gland. Three alkylthiouracils, namely, 6-*n*-

[24] Roblin, *Chem. Revs.*, **38,** 339 (1946). Trotter, *J. Pharm. and Pharmacol.*, **1,** 65 (1949).

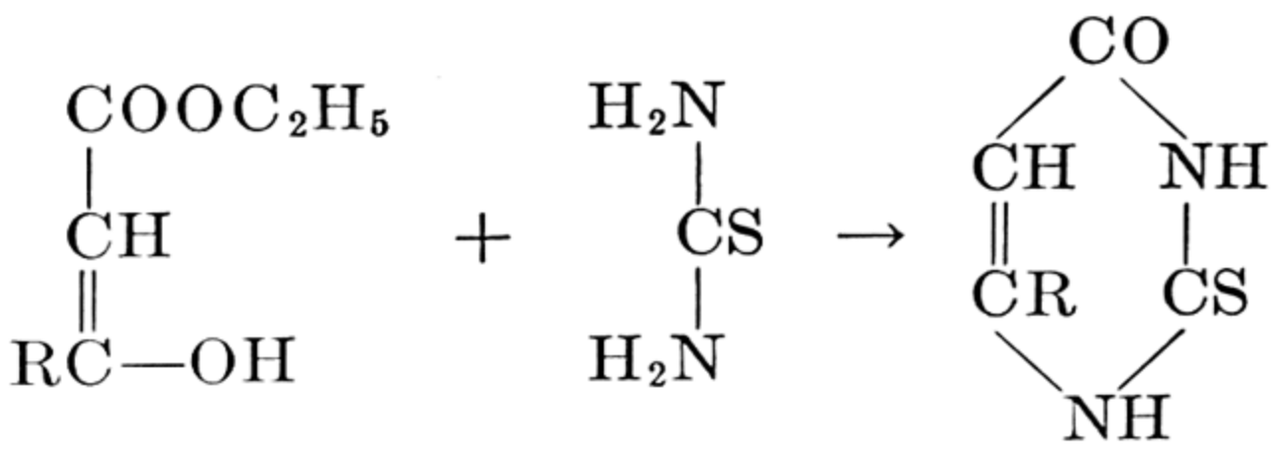
propyl-, 6-benzyl-, and 6-cyclohexylmethyl-2-thiouracil are more than ten times as active as the unsubstituted compound, and the margin of safety is increased three-fold in 6-*n*-propylthiouracil. The last two compounds are now the drugs of choice in this series of derivatives.

Aside from preparing patients for thyroidectomies, and reducing post-operative incidents by reducing the metabolic rate of the individuals, the thiouracils have also been able to replace thyroidectomy in cases in which operation is definitely contraindicated. In pregnancy the drugs may not be used because they pass into the fetus and inhibit the thyroid function of the latter.

All thiouracils cause agranulocytosis as a distinctively undesirable side effect. The loss of phagocytic power due to decrease of white blood cells must often be counteracted by penicillin until the white blood cell count has returned to normal.

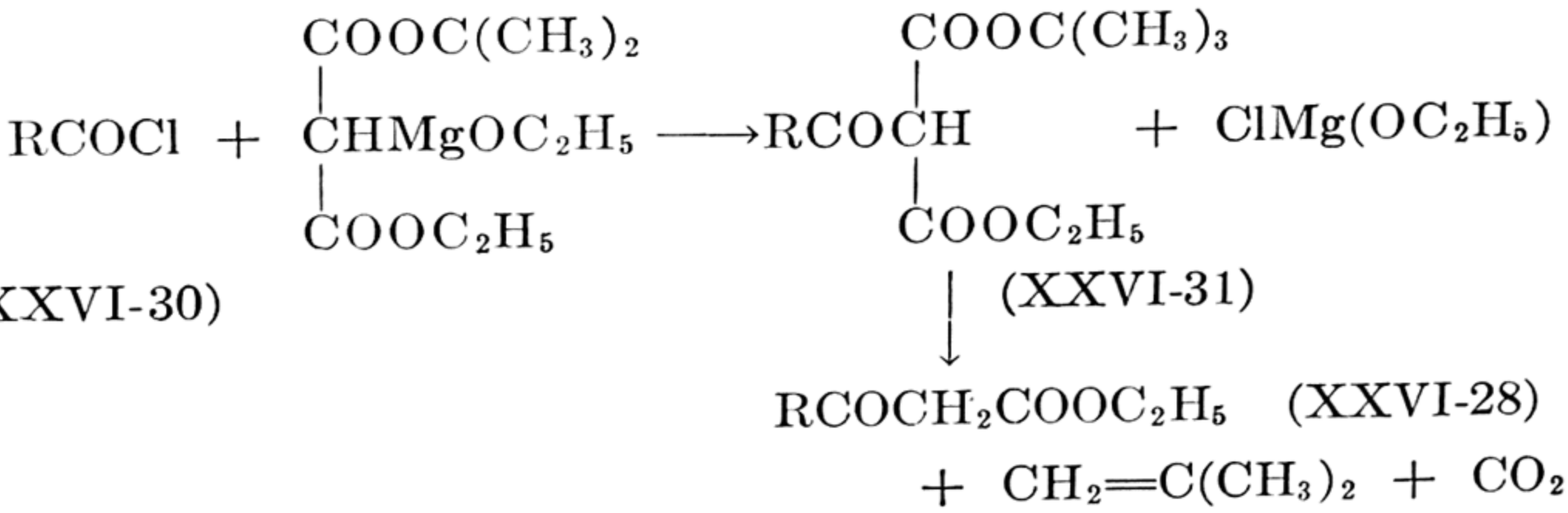
Table I lists some of these compounds and their activities. The field has been reviewed by Roblin and by Trotter.[24]

The thiouracil derivatives (XXVI-29) are synthesized from thiourea and β-keto esters (XXVI-28) with the aid of sodium ethoxide solutions:



(XXVI-28) (XXVI-29)

In turn, the keto esters (XXVI-28) are synthesized best by the ethyl *tert*-butyl malonate method according to the following scheme.[25] The acid



(XXVI-30) (XXVI-31)

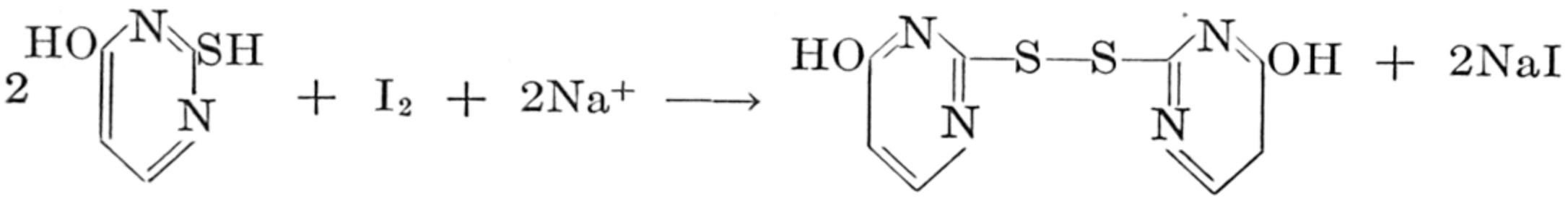
chloride (XXVI-30) reacts with the magnesium ethylate derivative of ethyl *tert*-butyl malonate,[26] and the intermediate acyl substituted malonate

[25] Anderson, Halverstadt, Miller, and Roblin, *J. Am. Chem. Soc.*, **67,** 2197 (1945).
[26] Breslow, Baumgarten, and Hauser, *J. Am. Chem. Soc.*, **66,** 1286 (1944).

(XXVI-31) is hydrolyzed and decarboxylated to the keto ester (XXVI-28) and isobutene. The availability of ethyl *tert*-butyl malonate is a factor limiting the size of the batches in this operation.

IX. MECHANISM OF ACTION OF THIOURACIL[27]

Thiouracil, and other thiourea-like substances are oxidized by iodine at neutral pH to disulfides (XXVI-32), at a rate too rapid to be measured accurately *in vitro*. It is likely that this rate is several hundred times the



(XXVI-32)

rate of the reaction of iodine and tyrosine. It may be assumed that the many thiourea-like substances which affect the thyroid gland compete with tyrosine for the iodine needed in the formation of diiodotyrosine, and thereby interfere with the synthesis of thyroxine.

Objections to this interpretation rest on the ability of many other thiols, such as thioglycollic acid, cysteine and glutathione, to react with iodine as rapidly as thiouracil or thiourea. Yet, these thiols do not interfere with iodine function. The cause of this inactivity may be due to differences in absorption and distribution; the inactive thiols may not reach the site of reaction in the thyroid cell, or else not reach it in the reduced thiol form. It would also be necessary for an active goitrogenic thiol to possess a high redox potential in order to survive other common biological oxidations and to influence effectively the high potential of the iodide-to-iodine oxidation.

Peroxidases would be the most likely enzymes to catalyze the oxidation of iodide ions to iodine. Thiols should therefore appear as specific inhibitors of such enzyme systems, or compete for the enzyme and be oxidized instead of iodide. An alternative function of the thiols in this reaction may involve competition for the available hydrogen peroxide so that none is available for the oxidation of iodide. Thiourea actually does inhibit peroxidase, in contrast to most sulfonamides which do not have this ability (see below).[28]

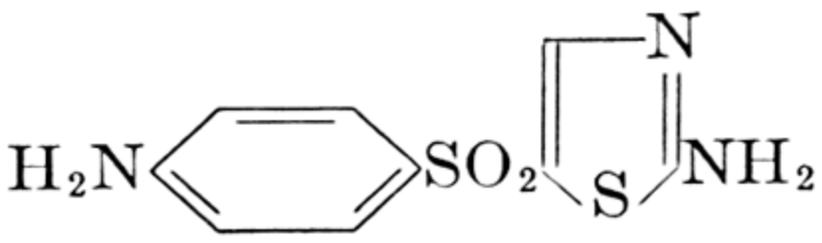
A model experiment both for the mechanism of the normal synthesis of thyroxine in the gland, and the inhibition of this synthesis by thiourea has been performed by Keston.[29] After adding radio-iodide and xanthine to milk, thyroxine containing radioactive iodine could be isolated from the

[27] Miller, Roblin, and Astwood, *J. Am. Chem. Soc.*, **67,** 2201 (1945).
[28] De Robertis and Grasso, *Endocrinology*, **38,** 137 (1946).
[29] Keston, *J. Biol. Chem.*, **153,** 335 (1944).

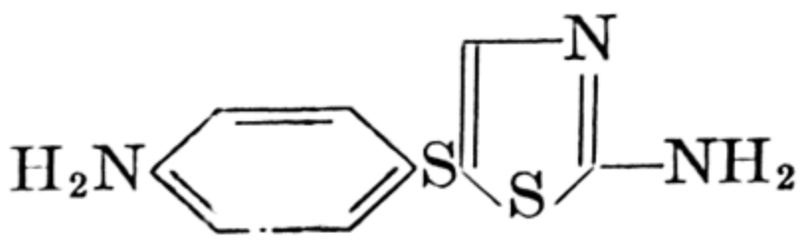
incubated liquid. It would appear that the xanthine-oxidase (a peroxidase) of the milk acted upon the added substrate, xanthine, and liberated hydrogen peroxide. The latter then oxidized iodide to the iodine needed for the iodination of the tyrosyl groups of casein. This reaction does not take place if thiourea is added before incubation.

None of these mechanisms could be applied to derivatives of aniline carrying acidic groups *para* to the nuclear amino group. Such compounds (*p*-aminobenzoic acid, many sulfanilamide derivatives, and derivatives of bis-(4-aminophenyl)sulfone) are difficult to iodinate, and could barely compete with enzyme systems for iodine. Some of these compounds inhibit dehydrogenases and peroxidases, but this is not a general phenomenon. Yet, most of them possess goitrogenic properties, and their activity has not yet been explained by a discrete biochemical mechanism.

In the group of sulfonamides, sulfathiazole, sulfapyridine and sulfadiazine are the most active hyperplastic agents, but none of them approach thiouracil and its congeners in activity. It is interesting to note that the activity of Promizole (XXVI-33), the most highly goitrogenic aromatic sulfone known, is only 18% that of thiouracil but its reduction product, the sulfide (XXVI-34), has an activity of 53%. One could theorize that goitrogenic activity is connected with bivalent oxidizable sulfur. This could not hold, of course for active aromatic amines, 4,4′-diaminodiphenyl-



(XXVI-33)



(XXVI-34)

methane (XXVI-35), and 4,4′-diaminobenzil (XXVI-36) which contain no sulfur atom.[14]

(XXVI-35)

(XXVI-36)

CHAPTER XXVII

Drugs for the Treatment of Cancer

I. TERMINOLOGY

The study of tumors in all their relations is the purpose of oncology. The term tumor or neoplasm stands for any circumscribed growth, arising from pre-existing tissues, but independent of the normal rate or laws of growth of the latter. Tumors do not have any physiological function; the alien cell does not have the vital activity of the communal cell from which it arises.

One generally distinguishes two types of tumors, benign and malignant. Benign tumors do not form metastases and are not transplantable. A metastasis is the appearance of tumors in parts of the body remote from the location of primary tumors. It is caused by a transport of tumorous tissue particles through lymph and blood vessels and is, in principle the same as a transplantation.

Depending on the anatomical location of tumor tissue, many alternate shorter terms are used to describe neoplasms. An adenoid tumor is called adenoma, an adipose tumor lipoma, an osseous tumor osteoma, a vascular tumor angioma, and so forth. More common are the distinctions between carcinoma and sarcoma. A carcinoma is a malignant cancer (χάφκινος, crab; (lat.) cancer) involving epithelial and endothelial tissue such as skin, glands, various ducts and tubes, the lining of the respiratory and digestive tracts, heart chambers, lymph and blood vessels. A sarcoma is a malignant tumor involving connective tissues, esp., bones, ligaments and tendons. The terms sarcoma and carcinoma are often combined under the heading of cancer.

II. ANTIMITOTIC AGENTS

Drugs which retard cell division, and damage tumor tissue are of interest in a potential control of cancer. They act by causing tumors to shrink, bleed or regress, or by decreasing the excessive number of white blood cells in leukemia which is classified as a cancer of the blood.

In order to develop fruitful ideas about the treatment of a disease, its cause must be understood. The causes of cancer are still unknown. Arising from normally growing cells which obey the laws of anatomical locali-

zation, new uncontrolled tumor cells begin to grow and spread in a haphazard irregular manner. The neoplasm formed by these cells behaves like a foreign material which cannot be integrated with normal tissues. Neoplastic cells metabolize carbohydrates in a manner differing from normal cells: they glycolyze under aerobic conditions while the normal cell glycolyzes only anaerobically.[1] In this respect, tumor cells resemble fast-growing embryonic cells, and it has been suggested that the cause of naturally occurring tumors in man and mammals, may be a regression in enzymatic complexity of the normal cells. Potter has found that oxalacetic oxidase is no longer available in the Krebs cycle of the cancer cell. On the other hand, nucleoproteins, ever-present in rapidly dividing cells, rise sharply in neoplastic tissues. One might conclude from these findings that interfering with enzymatic reactions in cancer would be a step in the wrong direction. Instead, cancer therapy should aim at building up enzyme systems.

III. CARCINOGENESIS

Malignant lesions can be produced experimentally in a number of ways. Whether any of them have a bearing on spontaneous (natural) carcinogenesis is not known.

1. Physical Agents

Any type of chronic irritation, such as heat and ultraviolet irradiation, can ultimately alter normal tissue functions, and kill tissues. Roentgen and γ-rays have been implicated definitely in this connection.

One of the effects of radiation appears to be a poisoning of sulfhydryl enzyme systems by oxidation which is similar to such oxidations by vesicants.[2]

2. Chemical Agents

The most spectacular results in producing tumors have been obtained in the work with polycyclic hydrocarbons and related heterocyclic condensed ring compounds. We owe these studies largely to Cook, Kennaway and to Fieser who have synthesized and tested hundreds of cancerogenic compounds and have been able to derive certain conclusions about relations of structure and tumor-producing ability, and about the metabolic fate and the detoxication of the irritant compounds in the animal body.

The cancer-producing properties of these compounds have been determined mostly in mice and rats. If administered orally with the animal's

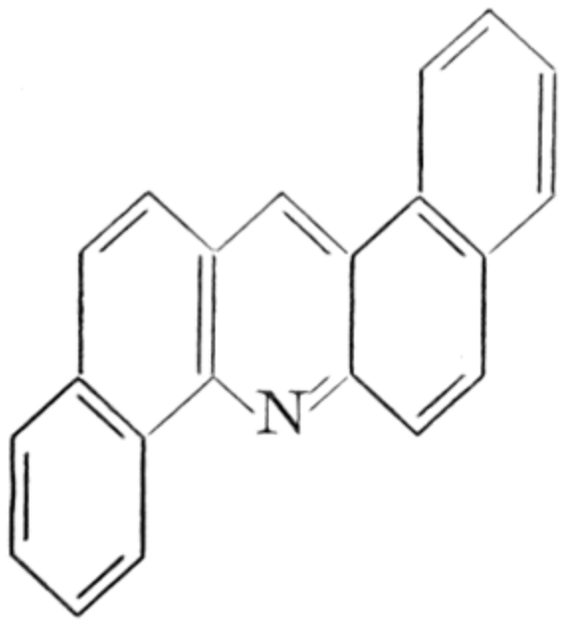
[1] Greenstein, *Biochemistry of Cancer*, Academic Press, New York, 1947. Mider. *Am. J. Med.*, **8**, 71 (1950).

[2] Barron, Dickman, and Singer, *Federation Proc.*, **6**, 236 (1947).

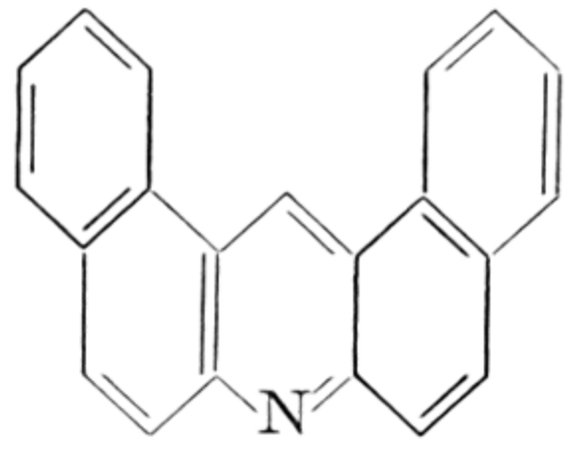
food, the active compounds cause carcinoma in the rat's stomach but not in the glands. If injected, sarcoma—cancer of the bones and connective tissues—results.

The number of potent tumor-producing synthetic hydrocarbons is too great to be listed here, and the subject of carcinogenesis transcends the scope of this volume. In Table I are listed only a few of these substances, and the time required to produce tumors.

Feeble but definite carcinogenic activity is exhibited by a few isologs of polycyclic hydrocarbons. Thus, 1,2,6,7-dibenzacridine (XXVII-1) and 1,2,8,9-dibenzacridine (XXVII-2) produce tumors after 13 months.

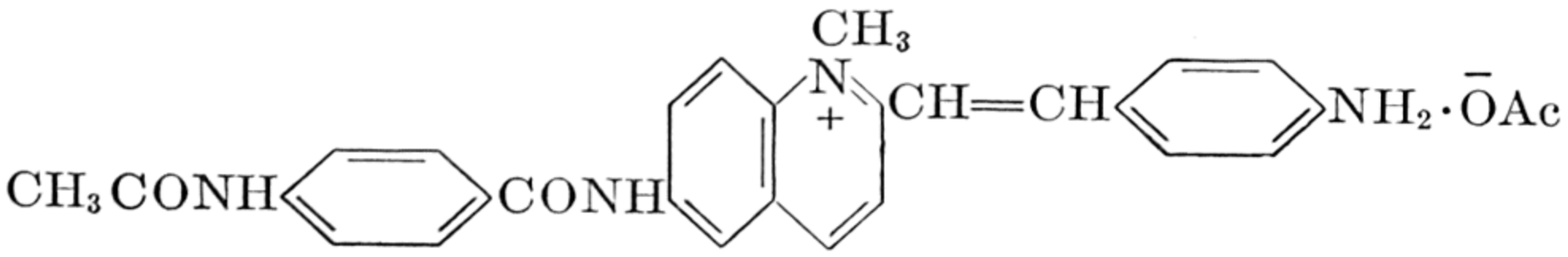


(XXVII-1)



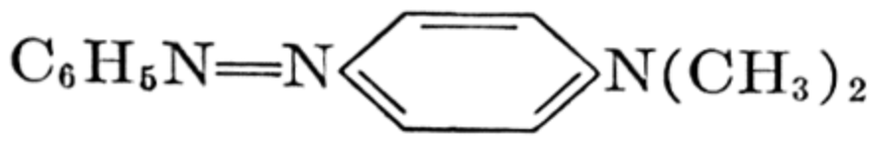
(XXVII-2)

Sarcomata have also been obtained after injection of 2-(*p*-aminostyryl)-6-(*p*-acetamidobenzamido) methylquinolinium acetate (XXVII-3).[3]

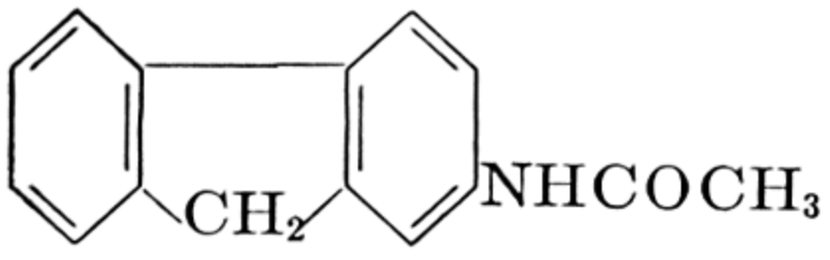


(XXVII-3)

Two other carcinogenic compounds must be mentioned here. 4-Dimethylaminoazobenzene (Butter Yellow, XXVII-4) is a powerful inhibitor of many enzyme systems and produces experimental tumors in laboratory animals. However, it would be faulty to assume that other enzyme inhibitors should also be carcinogenic. The second substance, 2-acetamidofluorene (XXVII-5) is distinguished by producing tumors in tissues distant from the site of injection.



(XXVII-4)



(XXVII-5)

[3] Browning, Cohen, Cooper, Ellingworth, and Gulbranson, *Proc. Roy. Soc.* (*London*), **B113,** 300 (1933).

TABLE I. SOME CARCINOGENIC HYDROCARBONS[4]

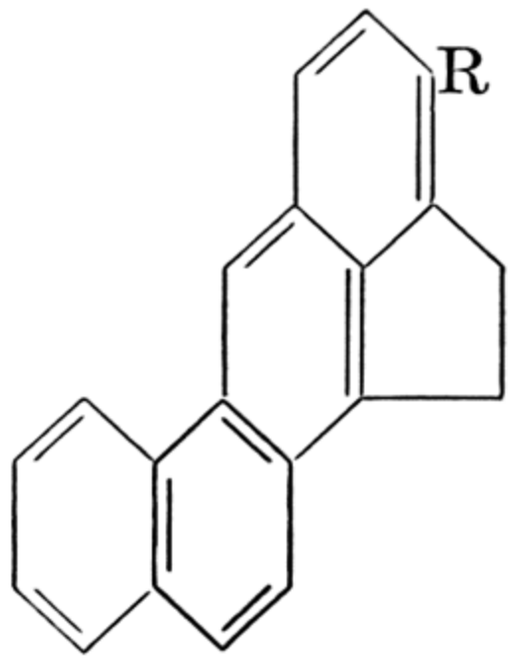
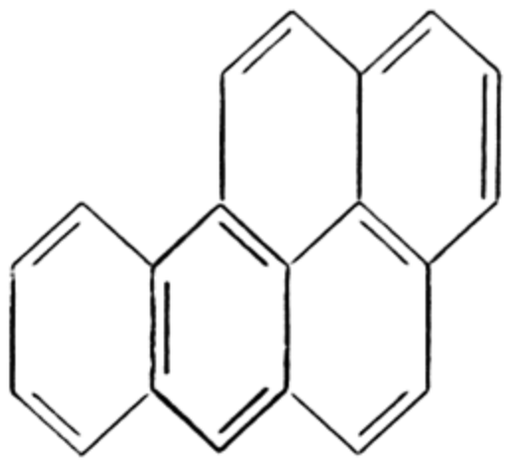
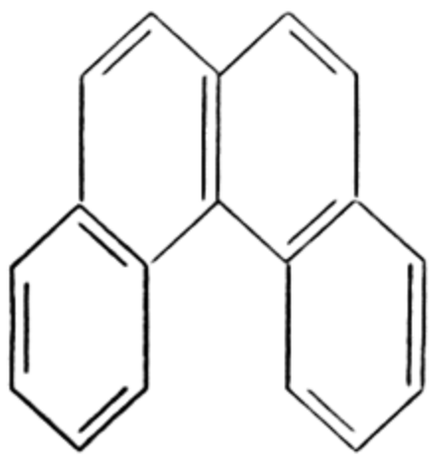
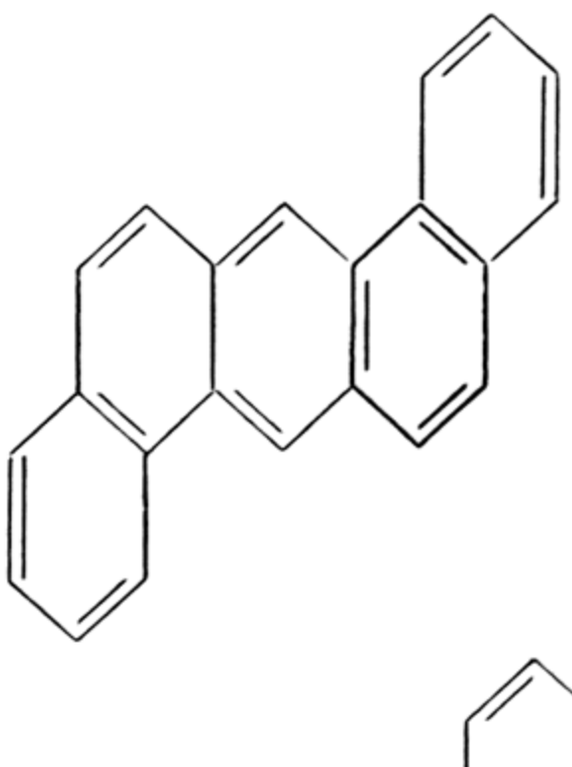
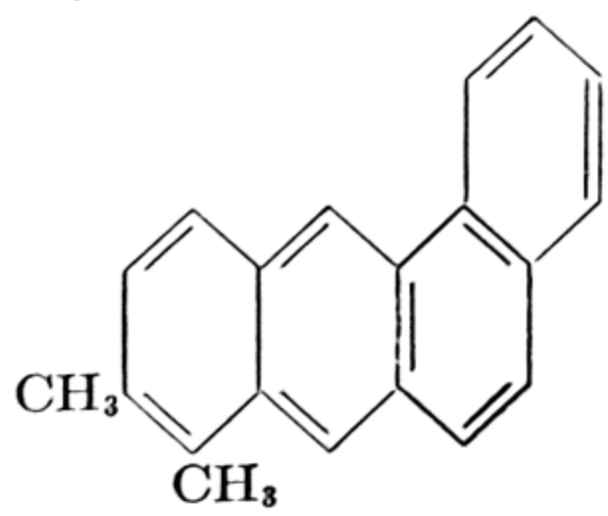
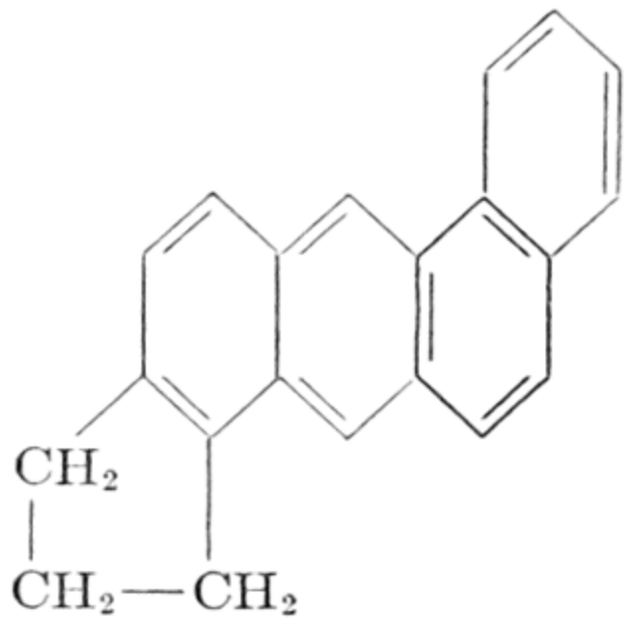
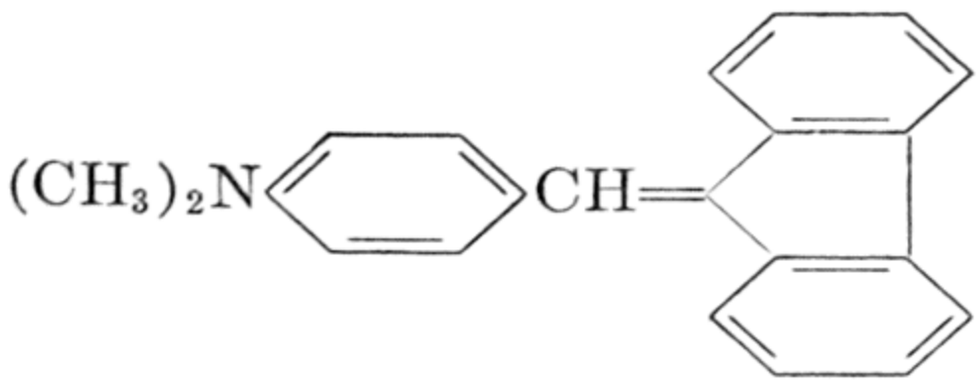
Name	Structure	Approximate time needed for carcinogenesis, months
Methylcholanthrene (R = CH_3) Cholanthrene (R = H)		2.2 — 5
Benzpyrene		5.7
3,4-Benzphenanthrene		12
1,2,5,6-Dibenzanthracene		4 — 8
5,6-Dimethyl-1,2-benzanthracene		8 +

TABLE I (*Continued*)

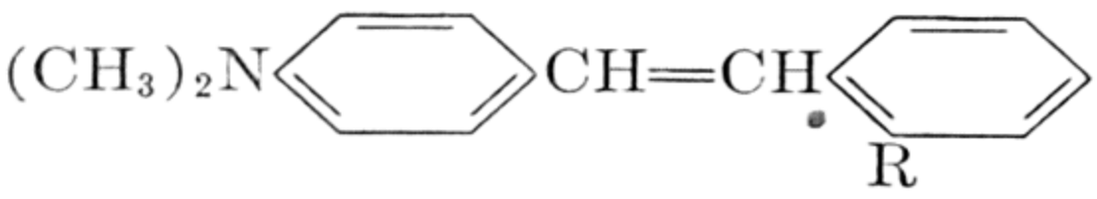
Name	Structure	Approximate time needed for carcinogenesis, months
5,6-Cyclopenteno-1,2-benzanthracene		8 +

Another fluorene derivative, 9-(4′-dimethylaminobenzal)fluorene (see XXVII-6), inhibits the growth of normal and of malignant tissue. The suggestion has been made that the association of growth inhibition and carcinogenic activity indicates that tumors may arise by adaptation of the normal cell to growth-inhibitory influences.

Overlapping of carcinogenic and carcinostatic properties have also been noted in the cases of 4-dimethylaminostilbene (XXVII-7) and 4-dimethylamino-2′-methylstilbene (XXVII-8).[5] Several other stilbene derivatives



(XXVII-6)



(XXVII-7), R = H
(XXVII-8), R = CH_3

having amino groups in *m*- and *o*-positions were inactive; it could be shown that all active compounds had the *trans* configuration in which the two benzene rings lie in one plane, and whose molecules are flat. Substituents which "buckle" the molecule reduced biological activity. In this respect the stilbene derivatives resemble the active carcinogenic hydrocarbons whose molecules also appear to have one common physical feature, namely, the so-called K region, a molecular section of high electron density, (the phenanthrene double bond of all active hydrocarbons).

[4] For details, see Fieser, *The Chemistry of Natural Products Related to Phenanthrene*. 2nd ed. pp. 88–93. Reinhold, New York, 1937.

[5] Haddow, Harris, Kon, and Roe, *Trans. Roy. Soc.* (*London*), **A241,** 147 (1948).

For details of this hypothesis, the review by Boyland should be consulted.[6]

The isosteric similarity of 4-dimethylaminoazobenzene (XXVII-4) and 4-dimethylaminostilbene (XXVII-7) should be noted in connection with their similar activity.

All chemical carcinogens are protoplasmic poisons which produce degenerative processes followed by increased cell growth activity. Papillomata appear slowly and cancer cells arise from these structures. If a solution of the carcinogen has been painted on the animal's ear, the time required for appearance of tumor cells can be shortened by punching the ear. Increased cellular activity is induced by the healing of the wound and tumors appear sooner. For dibenzanthracene, the incubation period is shortened from 16 weeks to 17 to 20 days.

The mechanism by which the structurally divergent carcinogens produce tumors is not known. The so-called cytogene theory holds that carcinogenic compounds influence the cytogene, a component of the cytoplasm of genes which collects in cell division. It then combines with ribonucleic acid and produces a plasmogene which can be regarded as an inheritable and self-perpetuating catalyst in the formation of enzymes characteristic of the particular cell.

3. Viroid Agents

A few cases of infectious transmissions of cancerous growth have become known. They are the Rous fowl sarcoma, the Brown-Pierce rabbit tumor, the rabbit myxoma and the Shofe papilloma. Recent reports that fungi have been found in a large number of cancers of all types need further confirmation.

There is at present no cause to assume that cancers are infectious. It is therefore questionable whether the term chemotherapy should be applied to the treatment of tumors with drugs. One can barely speak of chemotherapy in this case if the classical definition of Ehrlich's is regarded as final. Yet, many authors have used the term "chemotherapy of cancer", and the uncertainties concerning the origin of malignant neoplasms make a theoretical classification of antitumor drugs purely speculative. It may be argued that an enlarged thyroid gland also consists of new cells which can be made to regress by functional (antithyroidal) drugs. However, neoplastic cells are so different from those of an enlarged organ that remission of their growth and multiplication obeys entirely different laws. The terms tumor-necrotizing and antimitotic agents will be preferred for the purposes of this chapter.

[6] Boyland, *Ann. Rev. Biochem.*, **18,** 217 (1949).

4. Testing Methods

Additional differences of opinion in this field are introduced by the lack of unanimity among biologists as to the best test method for tumor-necrotizing drugs. Some investigators have used chick heart fibroblasts as test objects, but transplanted tumors in mice have remained the standard test objects. The activity of a compound is determined by microscopic examination of sections of artificial tumors in treated, and in control animals. Further trials are justified only with compounds which show microscopic evidence of potency in damaging tumor cells at dose levels which induce neither severe nor permanent injury to the host.

A typical screening procedure for antimitotic drugs[7] consists of suspending a mash of a recent, rapidly growing tumor graft in saline solution, and inocculating it into a leg of the animal by means of a syringe. Another sample of the mash is placed in a broth tube at the same time to establish sterility of the procedure.

Compounds to be tested are then injected into a different muscle at a dose just below the pre-determined LD_{50} for the initial test, and then at lower doses to determine the MED_{50}. Animals are killed 8, 20 and 48 hours after injection of the drug, and discoloration, necrosis or hemorrhage of the tumor are determined microscopically.

IV. THERAPY OF CANCER

1. Early Methods

External tumors were necrotized by the ancient Egyptians with mixtures containing arsenious oxide and in later centuries, zinc chloride as corroding agents. Some semblance of this procedure is still employed in some hospitals which have instituted an "escharotic" treatment of superficial tumors by topical application of necrotizing chemicals.

2. Toxins and Sera

In 1892, a patient suffering from inoperable sarcoma showed regression of the cancer after an attack of erysipelas. It was concluded that a bacterial toxin had "cured" the neoplasm. More recently, the possibility of using standardized bacterial toxins for the treatment of tumors was carefully re-investigated, and a 29% five-year survival among 312 cases of all types of inoperable cancer was observed.[8]

Roskin found that *Schizotrypanum cruzi* concentrated in the neoplasms of tumor animals infected with the parasite, and that the tumors softened and gave way slowly to healthy tissue. A vaccine prepared from heat-

[7] Hartwell, Shear, Johnson, and Kornberg, *Cancer Res.*, **6,** 489 (1946).
[8] cf. Hasegawa and Pfeiffer, *The Modern Hospital*, May, 1948.

killed trypanosomes (K-R vaccine, named after the discoverers, Klyueva and Roskin) was reported to have cured malignant growths in man. Other bacterial toxins, namely, diphtheria and tetanus toxins were said to cause regression of mouse tumors.[8] These findings need confirmation.

Other Soviet investigators around Skapier studied the role of the reticulo-endothelial defense system in the treatment of cancer. Working with anti-reticular cytotoxic serum (*A.C.S.*) they obtained favorable changes in Hodgkin's disease. This work also needs additional experimentation. This holds also for the studies of Amersbach who demonstrated complete disappearance of malignant lesions under the influence of extracts from normal spleen and liver.[8]

Certain tumors have been found to contain a spreading factor, perhaps the enzyme hyaluronidase to which their invasiveness of surrounding tissues has been attributed. Two anti-hyaluronidases, called antinvasins, have been discovered in plasma and have been studied for possible carcinostatic properties (see Chapter XXIX, Section II-2-f (2)).

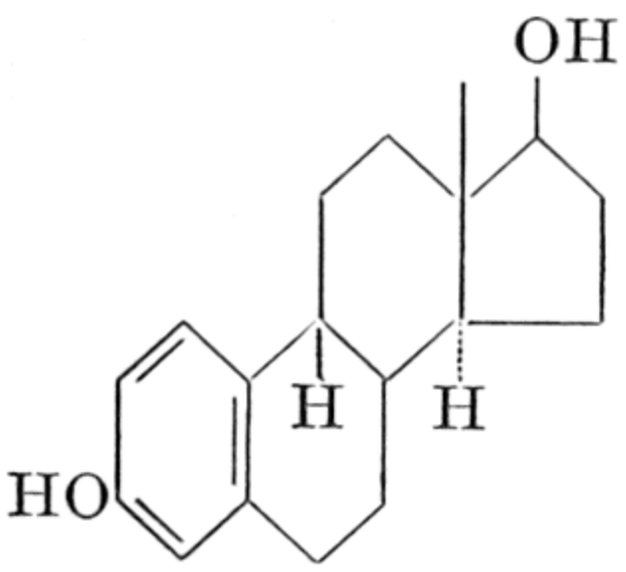
3. Sex Hormones

Both natural and synthetic sex hormones have the ability of inhibiting cell proliferation and have therefore been used in the treatment of human cancer. Regression of tumors of the sex and mammary glands, and of uterine malignancies has been attained in many cases. Treatment of certain tumors of this type with opposing sex hormones has become a routine clinical practice. Estradiol (XXVII-9) and stilbesterol (XXVII-10) both arrest the growth of prostatic cancers and their metastases in the male and relieve the pain caused by the pressure of these tumors on their surroundings. In males, estrogens also improve cancers of the bladder, and they are of benefit in mammary cancers in aged women. In younger women, they stimulate malignant growths. This overlapping of stimulatory and retarding properties can also be seen in animal experiments. Experimental mammary tumors have been produced by administration of pure estrogens to male mice, and, vice-versa, castration of female mice bred from a strain with a high incidence of cancer reduced drastically the cancer rate.[9] Curiously, rats are more resistant to the carcinogenic action of estrogens than mice, and other animals are completely resistant.

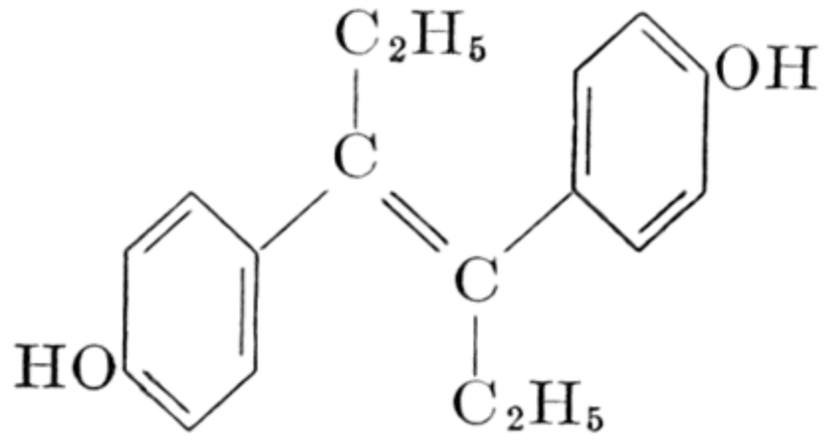
Mammary glands are not the only tissues affected by such experiments. Various tumors of male and female sex organs have been produced by the action of estrogenic hormones, and leukemia and lymphoid tumors have been observed following administration of estrogens to mice.

[9] Loeb, *J. Am. Med. Assoc.*, **104,** 1597 (1935).

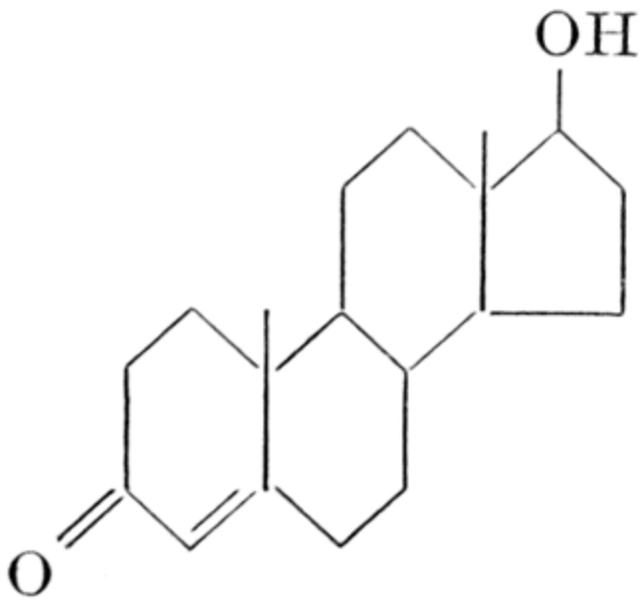
Certain mammary cancers regress under the influence of androgenic hormones, especially testosterone (XXVII-11). This hormone is usually administered intramuscularly in form of its propionate which is slowly absorbed from the site of injection, and then hydrolyzed. 17-α-Methyltestosterone (XXVII-12) shows equally good results in even smaller doses. The side-effects of the treatment—deepening of the voice, growth of hair on the face and body, etc.—are negligible in comparison with the relief from pain obtained.



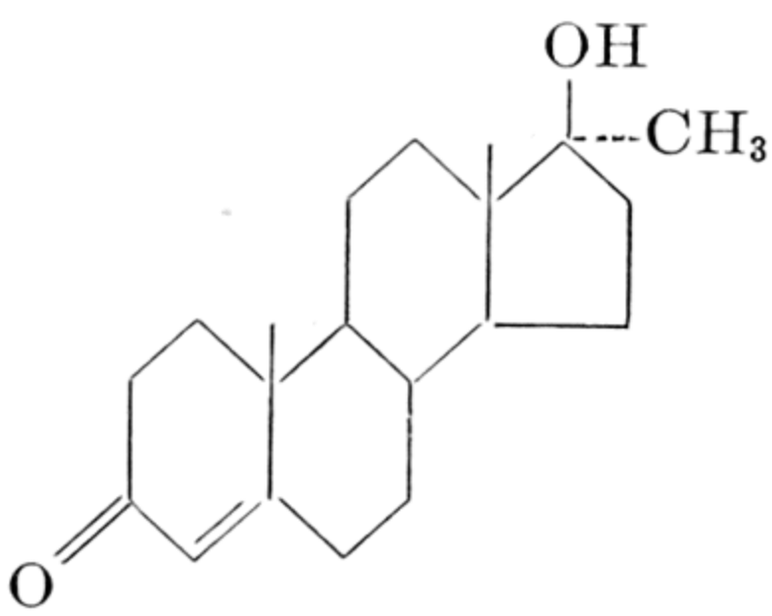
(XXVII-9)



(XXVII-10)



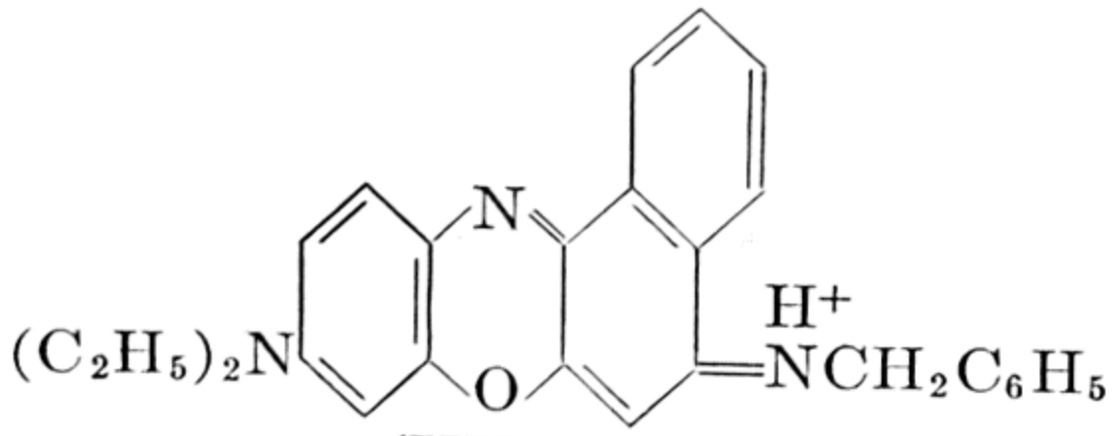
(XXVII-11)



(XXVII-12)

4. Dyes

Several dyestuffs which exhibit antiseptic and chemotherapeutic—that is, cell-growth inhibitory—properties retard the growth of malignant tumors. This is particularly pronounced in the oxazine dyes Nile blue A,



(XXVII-13)

and Nile blue B (5-benzylamino-9-diethylaminobenzo[a]phenoxazine; Colour Index No. 914)[10] (XXVII-13) which show the greatest staining and necrotizing activity for tumor tissue.[11]

5. Alkaloids and Alkaloidal Drugs

a. Colchicine

The alkaloid colchicine (XXVII-14), usually obtained by extraction of the seeds and bulbo-tubers of the autumn croccus, *Colchicum autumnale*, is a highly toxic substance which causes vomiting and nausea and paralysis of the central nervous system. Its salicylate has been used empirically in the treatment of gout, but the most interesting biological property of colchicine is its ability to inhibit cell division.

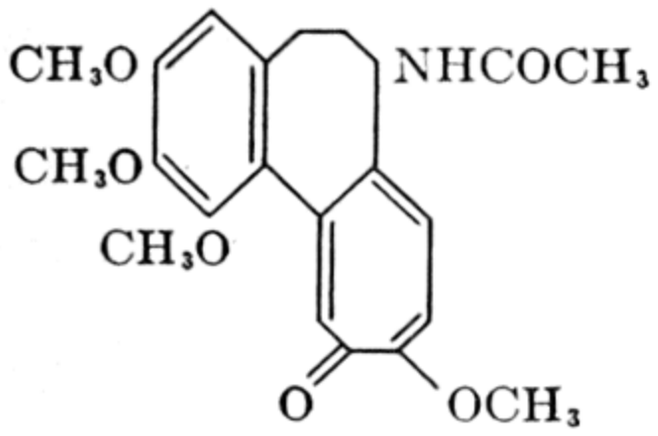
In a normally dividing cell, the number of chromosomes doubles; the chromosomes move toward opposite ends of the cell but remain connected by a bridge-like strand, the spindle. This structure then contracts and breaks and permits division of the cell into two daughter cells, each having the same number of chromosomes as the parent cell before the start of the dividing process. Colchicine acts by destroying the connecting spindle and thus preventing the formation of two daughter cells. The remaining cell now possesses the double number of chromosomes but is unable to divide (diploidism). This doubling of chromosomes can be repeated several times (polyploidism) without resulting in cell division, as long as the cell remains exposed to the antimitotic alkaloid. Finally, the undivided parent cell may become so filled with chromosome matter that it dies.

A similar alteration of chromosome characteristics underlies the antimitotic effect of colchicine on tumor cells. Unfortunately, the drug is not sufficiently specific for tumor tissue. Colchicine destroys also essential dividing cells in the crypts of the small intestine, lymphoid tissue and bone marrow, and in the mouse is more effective against normally growing cells than against implanted sarcoma 37 in these areas.[12]

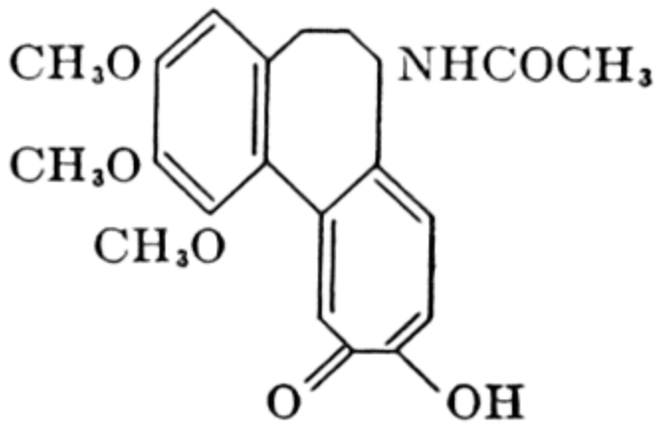
Colchicine causes a temporary fall in the number of leucocytes in leukemia but this is followed by a great rise of the white blood count.[13] It appears that mitosis is arrested half way, and that the partially divided cells simulate an increased number of leucocytes.[14]

[10] Soc. Dyers and Colourists, Colour Index, Great Britain, 1924.
[11] Lewis, Goland, and Sloviter, *Anat. Rec.*, **96,** 201 (1946). Sloviter, *Science*, **110,** 687 (1949).
[12] Clearkin, *J. Path. Bact.*, **44,** 469 (1937).
[13] Pernice, *Sicilia Med.*, **1,** 265 (1889). Dixon and Malden, *J. Physiol.*, **37,** 50 (1908). Eigsti, Dustin, and Gay-Winn, *Science*, **110,** 692 (1949).
[14] Lits, *Compt. rend. soc. biol.*, **115,** 1421 (1934). Ludford, *Arch. exp. Zellforsch.*, **18,** 411 (1936).

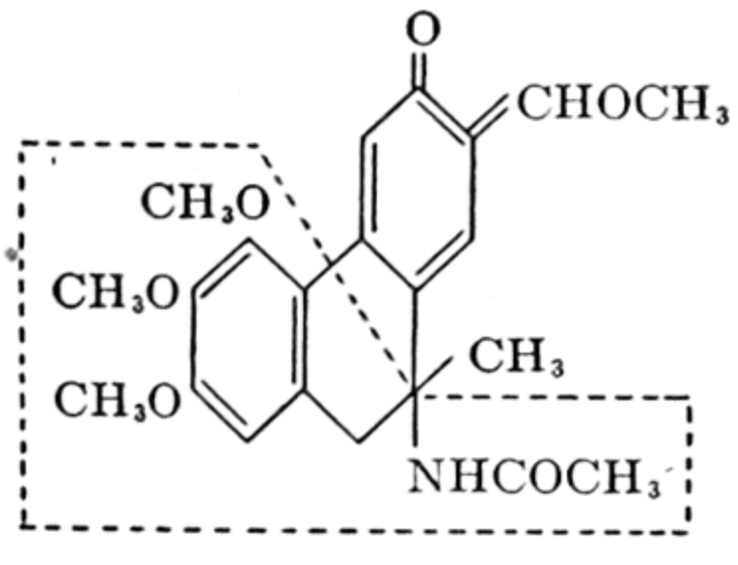
The formula of colchicine would furnish the logical point of departure for modifications of the structure of the alkaloid, designed to heighten antimitotic activity to useful non-toxic levels. Unfortunately, the exact structure of colchicine is not yet known.[15] Most workers now accept the formula proposed by Dewar (XXVII-14) which shows colchicine as a de-



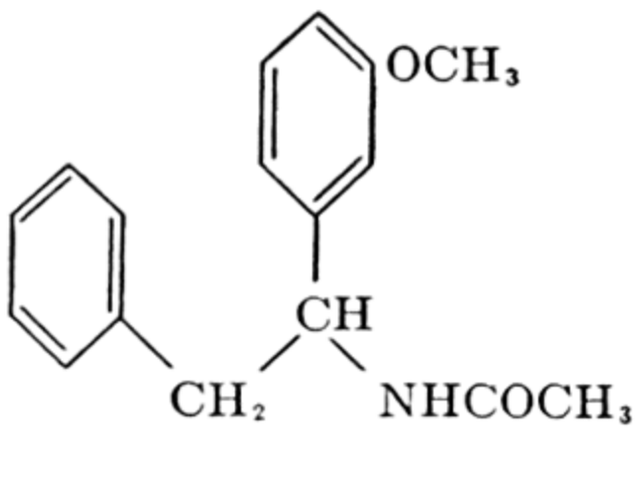
(XXVII-14)



(XXVII-15)



(XXVII-16)



(XXVII-17)

rivative of a methoxylated tricyclic condensed ring system containing two seven-membered rings, a keto and an α-enol ether group, with the nitrogen as part of an acetamide group.[16] The α-enolic ketone which can be obtained by demethylation is called colchiceine (XXVII-15). These formulas have superseded an older, now abandoned formulation of Windaus which pictured colchicine as a phenanthrene derivative (XXVII-16). This erroneous formula is reproduced here because it had an inadvertently important bearing on the further developments of antimitotic drugs.

b. Modifications of the Colchicine Structure

Simple alkyl ethers of colchiceine are less active than colchicine when tested for antimitotic action in chick fibroblasts.[17] Therefore, modifications were based on a functional version of the (wrong) Windaus formula

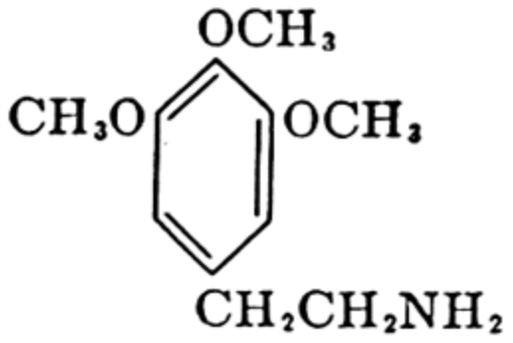
[15] cf. Henry, *The Plant Alkaloids*, 4th ed. Blakiston, Philadelphia, 1949, pp. 650–658.

[16] Dewar, *Nature*, **155,** 141 (1945).

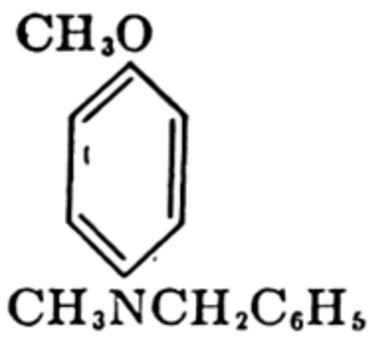
[17] Lettré and Albrecht, *Z. Physiol. Chem.*, **271,** 200 (1941). Lettré and Fernholz, *ibid.*, **278,** 175 (1943). Lettré, *Naturwissenschaften*, **30,** 34 (1942).

of colchicine. This was conceived essentially as a trimethoxyphenethyl derivative carrying alpha to the amino (or amide) group a ring structure which, for the sake of convenience may be pictured loosely as an aromatic nucleus (XXVII-17).

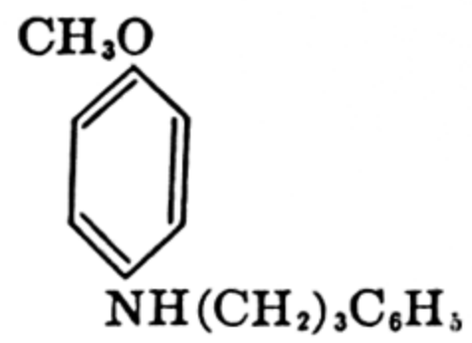
The significance of the trimethoxyphenethylamine portion of this prototype was tested first. It is represented in the alkaloid mescaline (XXVII-18) but this compound was inactive. However, its α-phenyl derivative (XXVII-19) did inhibit mitosis. This finding seemed to bear out the prediction, and several similar compounds were studied.



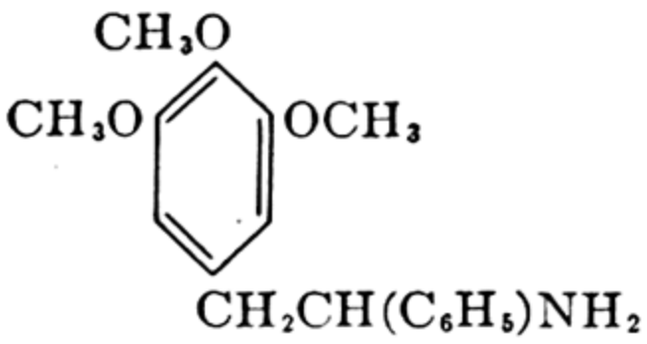
(XXVII-18)



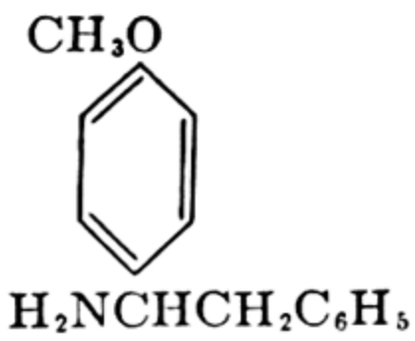
(XXVII-21)



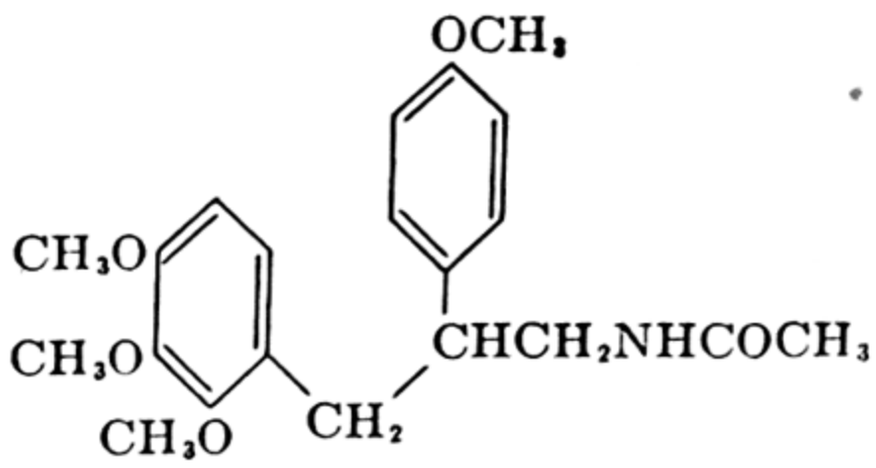
(XXVII-22)



(XXVII-19)



(XXVII-20)



(XXVII-23)

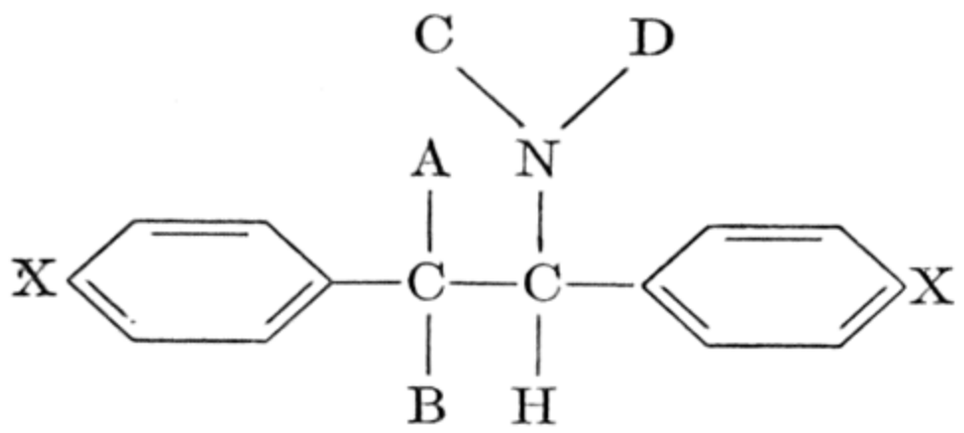
Apparently, a primary amino group was needed for activity since α-phenyl-β-(p-methoxyphenyl)ethylamine (XXVII-20) inhibited mitosis considerably while N-methyl-N-benzyl-p-anisylamine (XXVII-21) and N-(γ-phenylpropyl)-p-anisylamine (XXVII-22) were inactive.

In a closer approximation to the formula of colchicine N-acetyl-β-p-anisyl-γ-(3,4,5-trimethoxyphenyl)propylamine (XXVII-23) was tested and found to exert an abnormal influence on the mitosis of rat liver cells.[18]

Dodds and his coworkers[19] contributed to this group similar amines on the basis of a different approach. Remembering that the synthetic estrogen stilbesterol (XXVII-10) was developed by a spatial consideration of the formula of the natural sex hormone, estrone, an attempt was made to find a substitute for morphine (XXVII-24) by an analogous route. A number of derivatives of α-phenylphenethylamine (XXVII-25) were

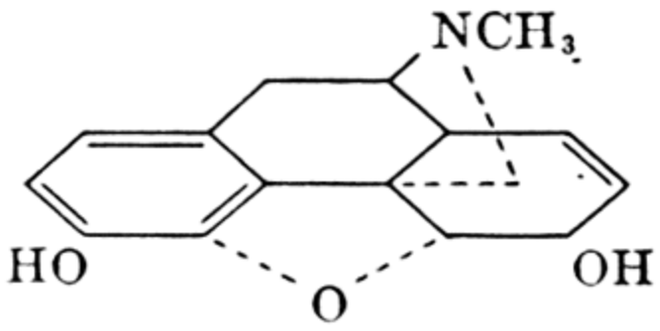
[18] Cook and Engel, *J. Chem. Soc.*, 198 (1940).
[19] Dodds, Lawson, and Williams, *Nature*, **154,** 514 (1944).

TABLE II. TUMOR NECROTIZING DERIVATIVES OF 1,2-DIPHENYL-2-AMINOETHANOL

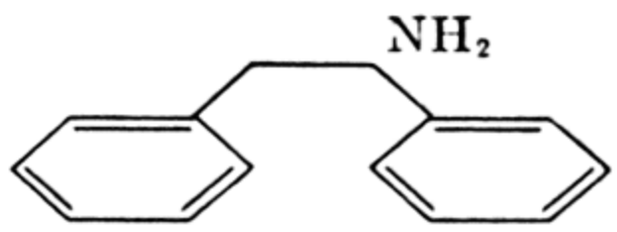


A	B	C	D	X	Y	Tumor Damage
H	OH	H	$(CH_2)_3CH_3$	H	H	+
H	OH	H	$CH_2CH_2C_6H_5$	H	H	+
H	OH		$-CH_2CH_2$ $\diagdown$ CH_2 $\diagup$ $-CH_2CH_2$	H	H	++
	=O	H	$(CH_2)_{11}CH_3$	H	H	+
	=O	H	$(CH_2)_3CH_3$	H	H	+
	=O	H	$(CH_2)_7CH_3$	H	H	+
H	OH	H	H	H	H	++
OH	H	H	H	H	H	++
H	OH	H	H	Cl	Cl	++
H	OH	H	C_6H_5	Cl	Cl	+
H	OH	H	$C_6H_4NEt_2(-p)$	H	H	++
H	OH	C_4H_9	C_4H_9	H	H	++
H	OH	H	$(CH_2)_2OH$	Cl	Cl	++
H	OH	C_2H_5	CH_2CH_2OH	H	H	++
H	OH		$-CH_2CH_2$ $\diagdown$ CH_2 $\diagup$ $-CH-CH_2$ $\vert$ CH_3	H	H	++
H	OH		$-CH_2CH_2$ $\diagdown$ CH $\diagup$ $-CH_2-CH$ $\vert$ CH_3	H	H	++

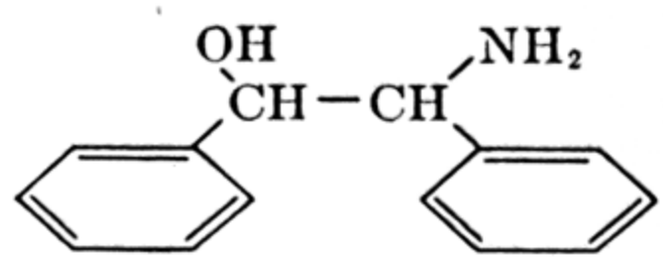
screened for analgetic action and two of them, the amine (XXVII-25) and 1,2-diphenyl-2-aminoethanol (XXVII-26) were studied more closely. These compounds relieved pain associated with nerve pressure, particularly with pressure caused by tumors, but were ineffective in other types of pain.



(XXVII-24)

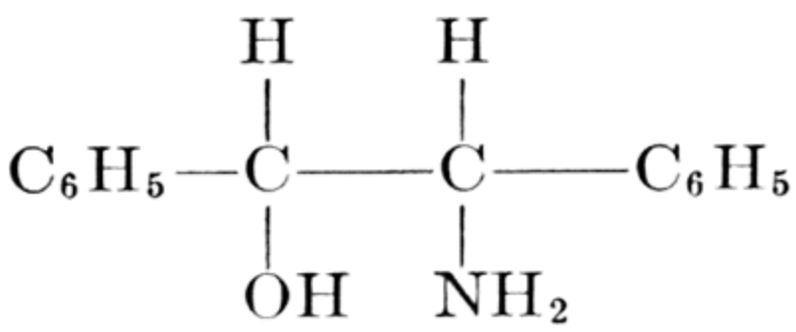


(XXVII-25)

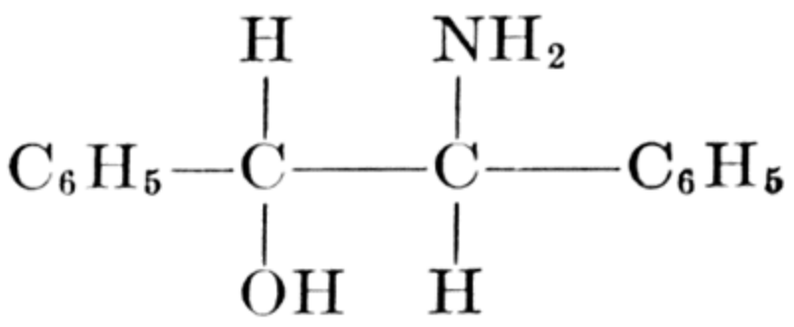


(XXVII-26)

The amine (XXVII-25) caused mental confusion while the amino alcohol (XXVII-26) had no undesirable side-effects. Later, it was found that only its "erythro" form (XXVII-27) is active whereas the "threo" diastereoisomer (XXVII-28) did not produce analgesia in cancer patients.[20]



(XXVII-27)



(XXVII-28)

Hartwell[21] expanded this series of amino alcohols and similar amino ketones and observed that some of them possessed antimitotic properties. Table II lists several of these compounds. The best tumor necrotizing agents in this series were compounds containing tertiary amino groups.



(XXVII-29)

A modification of the 1,2-diphenylaminoethanol structure is represented in quaternary methoxy-substituted phenacyl salts of heterocyclic bases such as *p*-methoxyphenacylpyridinium halide (XXVII-29) which necrotizes tumors.[22]

[20] McPhee and Erickson, *J. Am. Chem. Soc.*, **68,** 624 (1946).

[21] Hartwell and Kornberg, *J. Am. Chem. Soc.*, **67,** 1606 (1945). Compare also "Approaches to Tumor Chemotherapy," F. R. Moulton, Ed., Am. Assoc. Adv. Sci., Washington, D. C., 1947.

[22] Hartwell and Kornberg, *J. Am. Chem. Soc.*, **68,** 868, 1131 (1946). Shear *et al.*, in "Approaches to Tumor Chemotherapy," F. R. Moulton, Ed., Am. Assoc. Adv. Sci., Washington, D. C., 1947, pp. 236 ff.

c. Podophyllin

Podophyllin is the resinous extract of *Podophyllum*. Its chemistry,[23] and the relation of its constituents, podophyllotoxin and picropodophyllin have not been established beyond doubt. Tentative formulas are pictured in Chapter XVII (XVII-26 and 27).

Podophyllotoxin has recently been shown to be a potent tumor necrotizing agent, as are the α- and β-peltatins which are isomers of podophyllotoxin and can be separated from the toxin by chromatographic adsorption. Their active dose lies around 3 mg./kg. On the other hand, picropodophyllin is inactive.[24]

Although the proliferation not only of tumor tissue but also of normal tissue is inhibited by podophyllotoxin, the drug has been applied successfully as a topical necrotizing agent to condylomata acuminata (warty growths on the external sex organs or the anum).

These lesions can be cured readily by applications of solutions of the drug in mineral oil.

d. Radiation and Radioactive Compounds

Cancer can be both caused by, and treated with physical radiation and substances emitting radiant energy. Not only X-rays and radioactive rays, but even ultraviolet rays are capable of setting up chronic irritation which may ultimately result in leukemias.

X-rays have been used long and successfully for the treatment of carcinomata and sarcomata, and improvements and remissions have often been noticed. With the availability of radioactive isotopes from cyclotrons and atomic piles, the formerly expensive radium treatment has become widely applicable. Radiophosphorus (P^{32}), administered in the form of sodium monohydrogen radiophosphate, produces remissions in certain forms of leukemia, lymphosarcoma, Hodgkin's disease, multiple myeloma, and in another form of blood cancer, polycythemia vera. Radioiodine is concentrated in thyroid tissue and can be used in the treatment of thyroidal cancers. It is administered orally as sodium radioiodide containing I^{130} (half-life, 12.6 hours) and I^{131} (half-life, 8.0 days). Both isotopes emit β- and γ-rays.

[23] Späth, Wessely, and Nadler, *Ber.*, **66,** 125 (1933). Borsche and Nieman, *Ber.*, **65,** 1633 (1932). Hartwell and Schrecker, *Abstracts*, 117th Meeting A.C.S., Philadelphia, Apr. 10, 1950, p. 3K. Drake and Price, *J. Am. Chem. Soc.*, **73,** 201 (1951).

[24] Hartwell, *J. Am. Chem. Soc.*, **69,** 2918 (1947). Hartwell and Shear, *Cancer Res.*, **7,** 716 (1947).

Insoluble radiosalts are now often implanted as "seeds" in or near the malignant lesion, and exert an antimitotic effect during their life-time. Radiostrontium, Zn^{63}, radiomanganese, Au^{198}, Ag^{111}, Y^{91}, radiocobalt, Na^{24}, and Br^{82} are incorporated in such salts. Further uses of these new therapeutic tools have been mentioned in Chapter XXV.

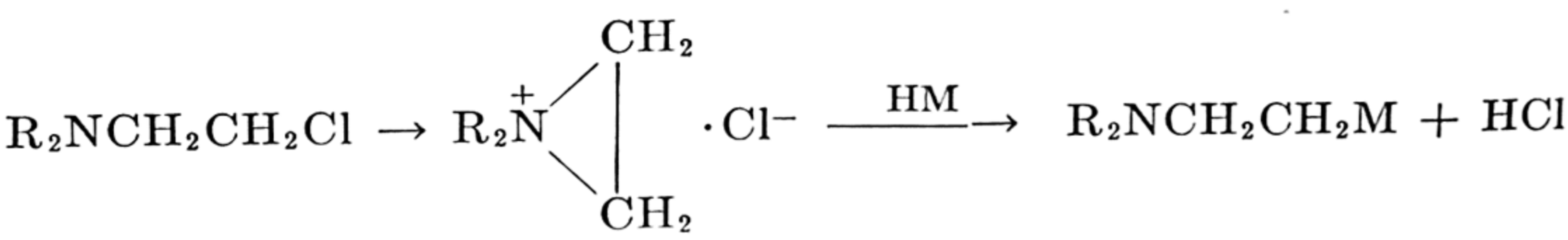
The use of radioactive isotopes in tumor therapy calls for certain exacting requirements. The isotope must be non-toxic in the necessary doses, and must be free from toxic impurities or daughter elements. It must not localize strongly in areas other than those treated, and its half life must be short enough so that radiation will not persist beyond the desired period. The maximum desirable half life may be taken as ten to fifteen days, and the workable minimum, as twelve hours.

e. Nitrogen Mustards

An indication that certain compounds can cancel out the carcinogenic effect of tumor-producing polynuclear hydrocarbons was obtained by the observation that small quantities of mustard gas almost completely inhibited the action of 1,2,5,6-dibenzanthracene.[25] The tissues treated with mustard gas [$(ClCH_2CH_2)_2S$] became refractory to the carcinogenic agent, and stayed this way until the inhibitor was no longer applied locally. There is no indication of a chemical reaction between mustard gas and dibenzanthracene, but the sulfide only makes the tissues temporarily less susceptible to the carcinogen.

Mustard gas is a vigorous and dangerous vesicant, and a search was made for analogous substances which could protect tissues from the effect of carcinogenic agents and lack, at least as much as possible, the blister-forming action of bis-(chloroethyl) sulfide. A few β-chloroethylamines, the nitrogen mustards, were singled out for closer study.

Compounds containing the β-chloroethylamine grouping Cl—C—C—N, have been discussed in connection with their application as sympatholytic agents (Chapter XX). They are stable as salts only; the free



(XXVII-30)

bases cyclize readily with the formation of ethyleniminium ions (XXVII-30). The latter act as alkylating agents, introducing the group $R_2NCH_2CH_2$— into a substitutable compound, MH. It is probable that

[25] Berenblum, *J. Path. Bact.*, **32,** 425 (1929); **34,** 731 (1931); **40,** 549 (1935).

they act by a similar mechanism in their second important pharmacodynamic behavior, namely in the arrest of malignancies.

The two β-chloroethylamines which have been most carefully investigated as antimitotics are methyl-bis-(β-chloroethyl)amine, $CH_3N(CH_2CH_2Cl)_2$ (XXVII-31), and tris-(β-chloroethyl)amine, $N(CH_2CH_2Cl)_3$. The former has been used more frequently; its non-vesicant hydrochloride is administered intravenously at a dose of 0.1 mg./kg. for four successive days.

The aliphatic β-chloroethylamines react readily with most cell constituents except unsubstituted sugars and fats, and they inhibit many enzyme systems, among them choline oxidase, cholinesterases and pyruvic acid oxidase.[26]

The two clinically useful nitrogen mustards produce favorable results in Hodgkin's disease, lymphosarcoma and early giant follicle lymphoma, especially if the lesions are so wide-spread that localized radiotherapy is impossible. Many other types of tumors and leukemias do not respond well. At best, there occurs temporary regression without lasting effects. The high toxicity of the β-chloroethylamines limits their use, and many oncologists prefer radiant energy to these drugs as a therapeutic tool.

f. Urethan

The use of urethan, $C_2H_5OCONH_2$, as a functional drug led to the incidental discovery of its remitting effect in leukemia.[27] Urethan is by no means a successful drug in any therapeutic application. Its toxicity is high, and interferes with the full utilization of urethan as an analgetic and hypnotic. It is useful at best when incorporated with quinine in solutions to sclerose varicose veins. When injected over long periods, urethan produces reduction of the white blood count in leukemia and other temporary improvements which can be obtained as well with deep X-ray therapy. Attention must be paid to experiments in rats in which urethan has produced lung tumors.

Urethan has a general cytotoxic effect on chick embryo fibroblasts in culture. Fewer cells enter mitosis, the intensity of the effect being proportional to the concentration of the drug. In addition, many non-dividing cells show degeneration.

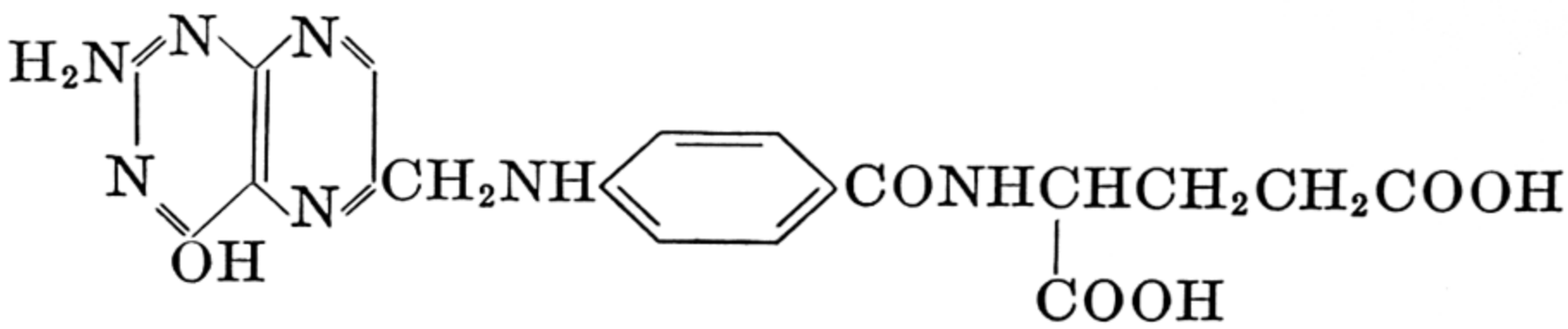
g. Pteroylglutamic Acid Antagonists

Among the most interesting researches in the field of antineoplastic agents are the investigations of metabolite antagonists of pteroylglutamic (folic) acid (XXVII-32). This compound, commonly abbreviated PGA,

[26] Boyland, *Brit. J. Pharmacol.*, **1,** 247 (1946). Fruton, Stein, Stahmann, and Golumbic, *J. Org. Chem.*, **11,** 571 (1946).

[27] Haddow and Sexton, *Nature*, **157,** 500 (1946).

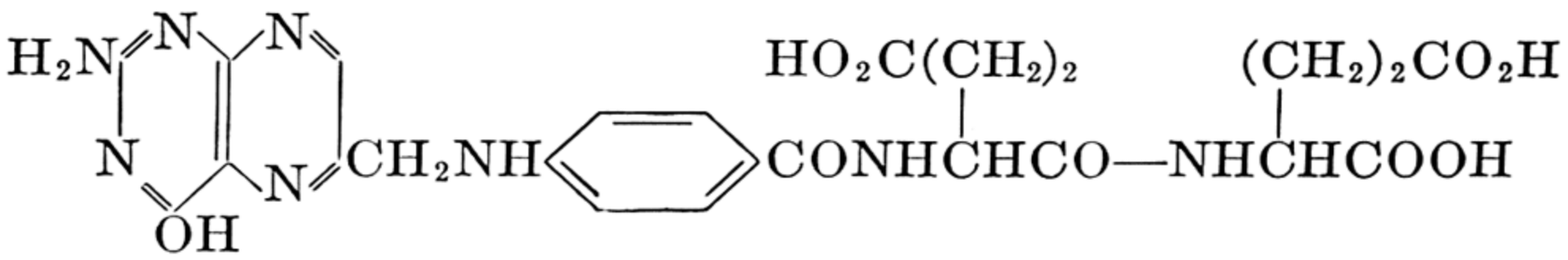
is an essential biocatalyst for normal blood cell formation (hematopoiesis) in animals and for the normal respiratory functions of these cells. It also is a stimulatory factor for several bacteria, particularly, *Lactobacillus casei*



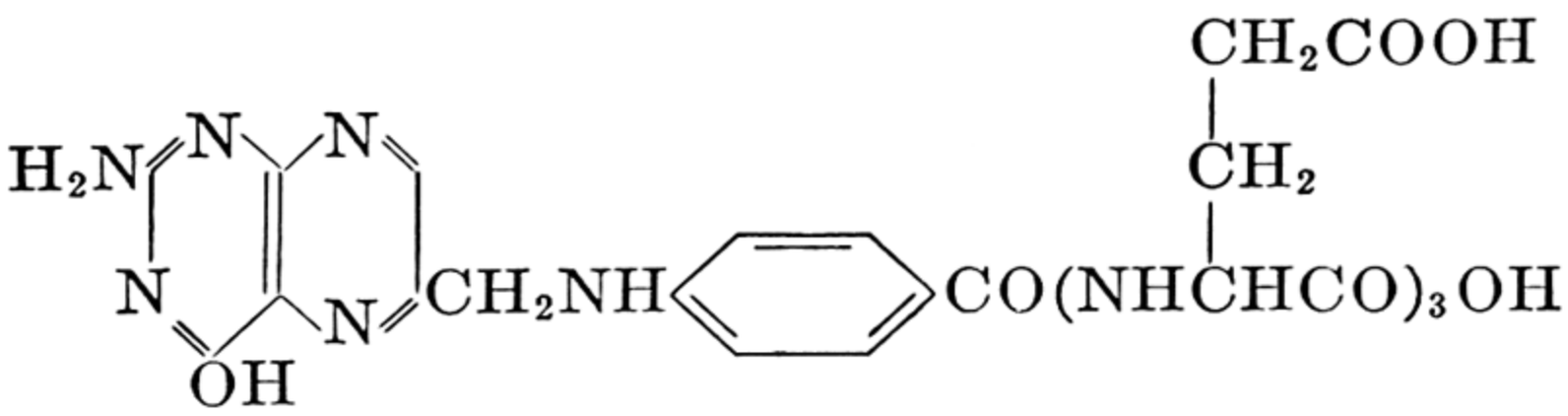
(XXVII-32)

and *Staphylococcus faecalis*. Folic acid has been used therapeutically in the control of certain anemias, and in tropical sprue (see Chapter XXVIII).

During the study of PGA it was observed that certain closely related derivatives could reverse the actions of the vitamin. Interest in these compounds was heightened when two naturally occurring glutamic acid conjugates of PGA were found to inhibit the growth of transplanted sarcomata.[28] These compounds were recognized as pteroyl-γ-glutamylglutamic acid (Diopterin, XXVII-33), and pteroyl-γ-glutamyl-γ-glutamylglutamic acid (Teropterin, XXVII-34) respectively.



(XXVII-33)



(XXVII-34)

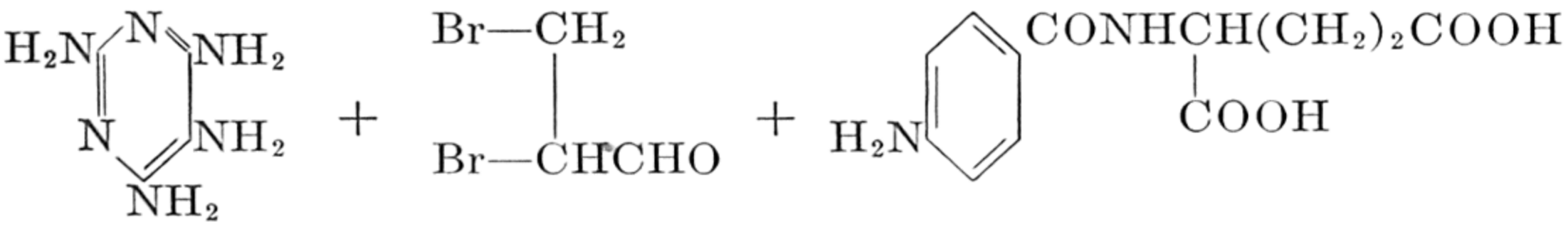
Diopterin produces remission of macrocytic anemia with megaloblastic arrest of the bone marrow. It relieves pain due to tumors but does not cure malignancies.

Teropterin relieves pain arising from the pressure of tumors on nerves in humans, and is said to have a moderate inhibitory activity on spontaneous mammary tumors in mice. It is interesting to note that Teropterin is the only of the five possible pteroyltriglutamic acids which exhibits such activity.

[28] Leuchtenberger, Lewisohn, Laszlo, and Leuchtenberger, *Proc. Soc. Exptl. Biol. Med.*, **55**, 204 (1944).

The myeloid cells of the bone marrow which produce white blood cells depend on pteroylglutamic acid (PGA) for their normal respiratory functions and are the most sensitive indicators of pteroylglutamic acid deficiency. Histological examination of the bone marrow reveals PGA deficiency before any other avitaminosis symptoms are observable, especially retardation of growth and an altered blood cell picture. It has therefore been suggested that PGA antagonists might be used in the control of leukemia originating in the malignant growth of myeloid cells. Of these antagonists, Aminopterin (XXVII-35) has proved the most satisfactory agent. It produces temporary remissions in acute leukemia in children.[29]

Aminopterin is 4-aminopteroylglutamic acid (XXVII-35). It was synthesized from 2,4,5,6-tetraaminopyrimidine (XXVII-36), 2,3-dibromopropionaldehyde (XXVII-37) and *p*-aminobenzoylglutamic acid (XXVII-38) under the conditions described for the synthesis of pteroylglutamic acid (Chapter XXVIII).[30]



(XXVII-36) (XXVII-37) (XXVII-38)



(XXVII-35)

The effect of Aminopterin on transplanted tumors has been investigated a number of times.[31] PGA progressively cancels the inhibitory action of this antagonist. Aminopterin was the most marked and consistent tumor necrotizing agent in a series of more than 250 compounds which included carbamates, derivatives of fluorene, nitrogen mustards and quinones. It was active under conditions in which Diopterin and Triopterin exhibited no apparent antineoplastic activity. However, the high toxicity

[29] Farber, Diamond, Mercer, Sylvester, and Wolff, *New Engl. J. Med.*, **238,** 787 (1948). Meyer, *Trans. N.Y. Acad. Sci.*, **10,** 99 (1948).

[30] Angier *et al.*, *Science*, **103,** 667 (1946). Seeger, Smith, and Hultquist, *J. Am. Chem. Soc.*, **69,** 2567 (1947).

[31] Schoenbach, Goldin, Goldberg, and Ortega, *Cancer*, **2,** 57 (1949).

of Aminopterin has kept this drug from becoming an important therapeutic agent.

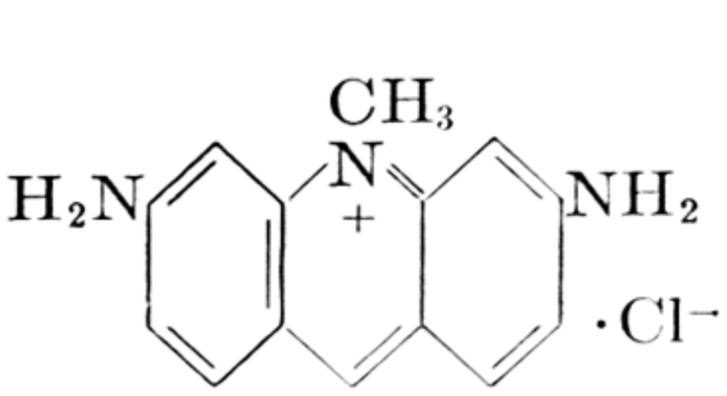
A number of pteroylglutamic acid antagonists have been screened for their ability to inhibit the reproduction of microorganisms, rather than for their cancer growth inhibiting power. This aspect of their activity is being treated in Chapter XXXII in connection with other metabolite antagonists.

h. Riboflavin Antagonists

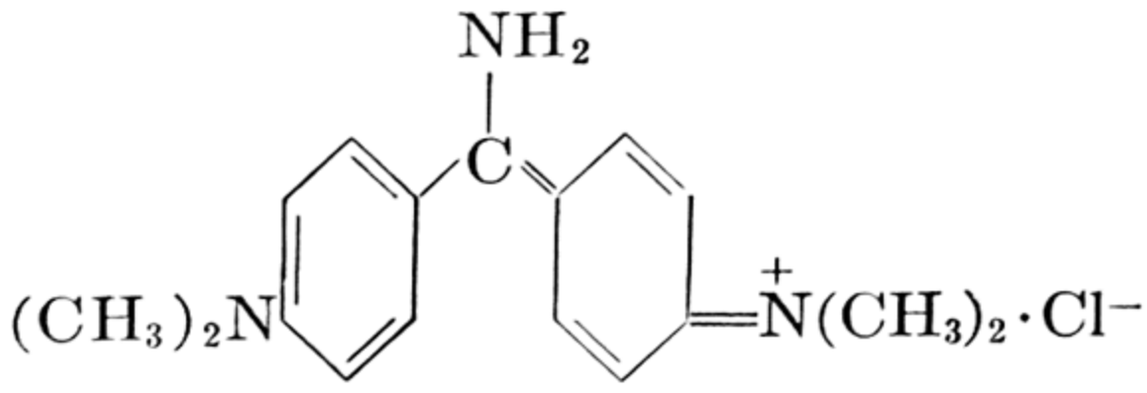
Based on the observation that complete regression of lymphosarcoma implants could be obtained in mice following temporary induction of riboflavin deficiency,[32] the effect of known riboflavin antagonists on tumor cells has been studied. Both isoriboflavin (XXXII-17) and D-galactoflavin (XXXII-19) make mice refractory to further implantation of tumors when administered in large doses. See Chapter XXXII.

i. Miscellaneous Compounds

So many different substances have been screened for their ability to necrotize tumors and to decrease the number of leucocytes in leukemia, that a selection appears rather futile. Most of them have been judged only by cytological criteria as being effective inhibitors of normal cell division, but some of them have been shown to retard successfully the growth of tumors. Acriflavine (XXVII-39) and sodium cacodylate (XXVII-40) belong to the first group, and the dye Auramine (XXVII-41) is also active against dividing cells. Another compound in which two



(XXVII-39)



(XXVII-41)

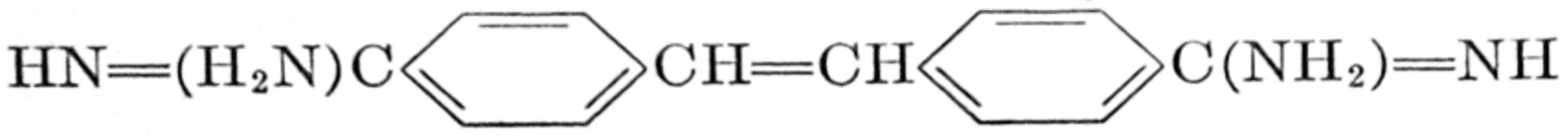
$(CH_3)_2AsO_2Na$

(XXVII-40)

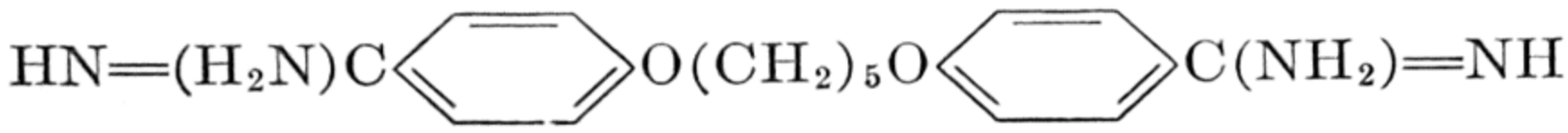
basically substituted aromatic nuclei are connected in their *para*- positions by an unsaturated bridge is stilbamidine (XXVII-42, 4,4′-diamidinostilbene); its main use is in the treatment of human leishmaniasis (Chapter XXXVII) but it has also been found to arrest temporarily the spread of multiple myeloma, a form of bone cancer. Its analog, pentamidine (4,4-

[32] Stoerk and Emerson, *Proc. Soc. Exptl. Biol. Med.*, **70**, 703 (1949).

(pentamethylenedioxy)dibenzamidine, XXVII-43) is as effective as stilbamidine in this condition. These amidines inhibit the glycolysis of tumor cells.



(XXVII-42)



(XXVII-43)

As in other fields involving redox systems, quinonoid compounds, or substances having the reducible group —OCCH=CHCO— have shown activity as antimitotic agents. Maleic acid inhibits division of chick fibroblast cells at a concentration of 0.3×10^{-6} M, but fumaric acid is inactive. That dehydrogenases are involved in these reactions is shown by the fact that 1,4-naphthalenediol diphosphate is active at a molar concentration of 5×10^{-10} while 1,4-naphthalenediol monohydrogen-succinate which can no longer be diphosphorylated exhibits no activity.[33]

[33] Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, **3,** 263 (1948).

CHAPTER XXVIII

The Vitamins

I. VITAMINS AND HORMONES AS MEDICINAL AGENTS

The distinction drawn between the action of a hormone, and that of a compound foreign to the body, but producing similar effects, breaks down immediately when a continuous series is available."

BARGER *and* DALE, *J. Physiol.*, 41, 84 (*1910*)

Vitamins and hormones are organic compounds which perform, in the organism, specific and vital functions in relatively small concentrations. They are required for normal growth and health of animals and man. They generally must be synthesized by anabolic processes while they are present within the organism. Otherwise, there is no [illegible]. Both types of substances are essential for the [illegible] energy and are not utilized as [illegible] the organism.

The relationship between vitamins and the endocrine glands is emphasized by the fact that certain vitamins [illegible] and are for them hormones. Both [illegible] there for proper functioning [illegible] be synthesized by the [illegible] and cannot be metabolized. Thus, [illegible] immediately concerned with the [illegible].

[illegible] between vitamins and hormones [illegible] synthesized by the living organism [illegible] of these factors. The [illegible] and health [illegible] glands [illegible] the whole endocrine [illegible] endocrine gland can substitute to a [illegible] deficiency of another one in an attempt to [illegible]. The mutual interdependence of particular [illegible] immediately influenced by endocrinal reactions.

[illegible] of vitamins and hormones [illegible] deficiency symptoms [illegible] growth is retarded, the adult organism begins to age

prematurely, and for each deficiency a specific syndrome of pathological manifestations is observed.

Absence of vitamins does not necessarily mean lack of these substances in the diet. Some individuals lose the ability to absorb and utilize the essential catalysts even if their diet contains the normally required amounts. The administration of large doses of vitamins can sometimes overcome this condition; even if part of the dose is not absorbed or metabolized faultily, there is enough left to take over the normal function of the vitamin. At this point it is no longer possible to draw a line between drugs and vitamins. The prevention or the cure of a typical vitamin deficiency (avitaminosis) by administration of vitamins is entirely analogous to the prophylactic or therapeutic action of a drug.

The same analogy holds for hormonal medication. If a damaged endocrine gland no longer produces adequate amounts of its specific hormones, serious metabolic disturbances of the whole organism will set in, usually concentrated in a characteristic deficiency disease. Administration of the missing hormones usually ameliorates or terminates this condition. Since the body may not be able to resume hormone synthesis, medication with the needed hormones may have to continue for an indefinite period.

The distinction between vitamins and hormones on the one hand, and drugs on the other hand becomes even less pronounced if one considers that at least fourteen vitamins and nine hormones can now be manufactured synthetically, and others may be added to this list shortly. Moreover, whereas most of the vitamins are unique in their specificity, a few (e.g., vitamin K, niacinamide) can be replaced by chemically closely related substances. This possibility can be realized even more in the series of the medullary adrenal, and of the steroid hormones. Here, considerable variation in chemical structure can be undertaken without loss of hormonal specificity, and in some cases synthetic variants have proved superior to the natural hormones. Several of the sympathomimetic derivatives of phenethylamine, the quaternary analogs of acetylcholine, and methyltestosterone can be cited as examples of drugs with improved hormonal activity.

Wide structural variations are possible for vitamins if not their regulatory specificity in higher animals, but their ability to support normal metabolism and reproduction of microorganisms is considered. Monocellular organisms, particularly bacteria, are much better equipped to handle nutritional deficiencies than more complex plants or animals. If vitamins are lacking in their nutrient, they can often synthesize the missing metabolite themselves and thus create their own essential catalysts. Or else, their enzymes can adapt themselves to the utilization of structurally

related substances which have been added to bacterial culture media. These experiments also provide a suitable proving ground to explore the limits of structural variation which will still produce substitutes for natural vitamins. It has been possible in many cases to construct anti-vitamins which inhibit microbial reproduction; such compounds have provided guiding thoughts in the field of chemotherapy. This question will be considered in detail in the chapter on metabolite antagonists.

The literature of vitamins and hormones is extremely extensive, and it would be impossible to deal with the many ramifications of these biological factors. Only their therapeutic uses can be discussed here and those chemical and biochemical aspects which have attracted the attention of medicinal chemists in recent years. Because the synthetic and manufacturing methods have been reviewed repeatedly, only a selection of the principal modes of total or partial syntheses will be shown in schematized form. For details, the reader is referred to the original literature.

The excellent monograph by Rosenberg* provides almost all the information on vitamins in one volume. The steroid vitamins and hormones have been reviewed authoritatively by Fieser and Fieser.*

II. THE VITAMINS

1. Vitamin A

Vitamin A (Carenol, Axerophthol) occurs only in the animal organism and has not been found in plants. It is stored mainly in the liver, and to a small extent in the lungs and kidneys. It is present both as the free alcohol and in the form of esters of palmitic and other higher fatty acids. The chief commercial sources of vitamin A are fish liver oils, from which the vitamin and its esters are now isolated by the Hickmann modification of molecular distillation in which the oil is spread continually as a thin film on carefully preheated disks rotating in a high vacuum.

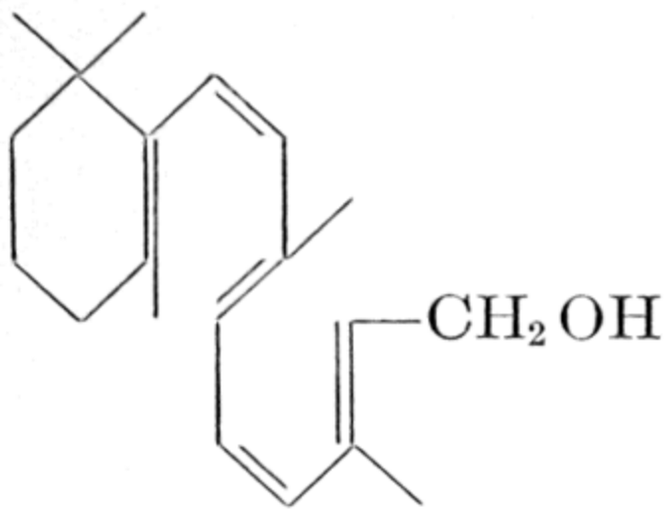
For pharmaceutical purposes, fish liver oil concentrates of high potency are commonly used if pure vitamin A is not available. The oils from shark, halibut, cod and percomorph are among the most rewarding products. The concentrates are virtually free from fishy taste and odor and provide adequate amounts of vitamin D as well as vitamin A.

Vitamin A has the formula (XXVIII-1).[1] It occurs together with its geometrical isomer, neovitamin A, in an approximate ratio of 1:2. Vitamin A is believed to have a *trans*-configuration about each double bond

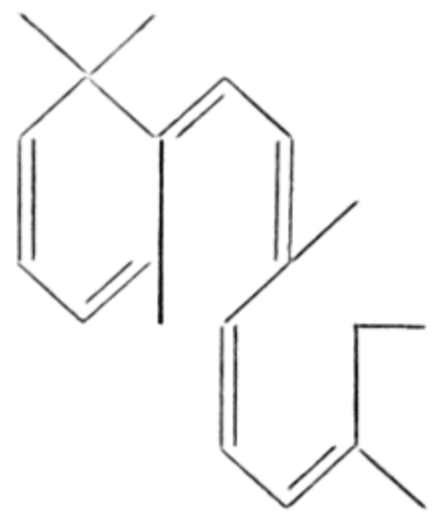
* Rosenberg, *Chemistry and Physiology of the Vitamins*, Interscience, New York, 1942. Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, New York, 1949.

[1] Karrer, Morf, and Schöpp, *Helv. Chim. Acta*, **14,** 1431 (1931).

while in neovitamin A the double bond of the allyl alcohol group is *cis*. The isomers have been converted into each other.[2]



(XXVIII-1)



(XXVIII-2)

Vitamin A is accompanied, in some fish liver oils, by similar compounds, anhydrovitamin A (potency, about 0.005% of XXVIII-1), and vitamin A_2 (XXVIII-2,[2a] potency, 38% of XXVIII-1). Pure crystalline vitamin A and neovitamin A have a biological activity of 334×10^4 International Units (I. U.) per gram. The U. S. P. Unit is equivalent to the I. U. and corresponds to the vitamin A activity of 0.6 γ of pure β-carotene in a standard test. The optimum requirement for an average adult lies around 1.5 γ of vitamin A per day.

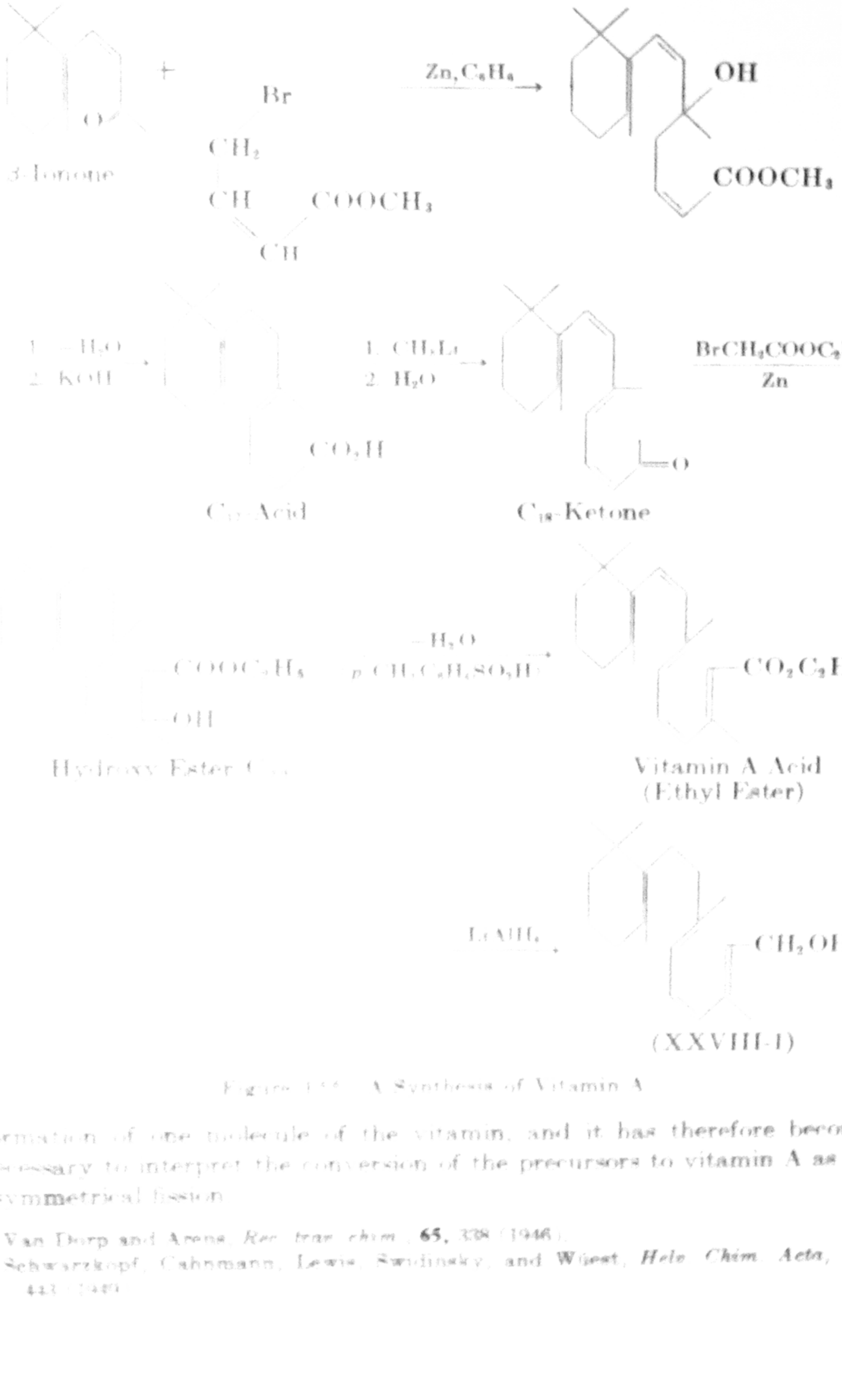
Vitamin A has been synthesized by a number of routes[3] but only one recent commercial method starting from β-ionone and methyl γ-bromocrotonate shall be represented diagrammatically in Figure 1. The overall yield in this synthesis is 54% of vitamin A_1 based on the C_{18}-ketone.

Normal nutritional requirements of vitamin A are satisfied by ingestion of pigments of the carotene group, the so-called provitamins A which are transformed to vitamin A in the human or mammalian liver or intestinal wall. There are eleven orange to red vegetable pigments which act as provitamins A. The formulas of three of them are shown below (α-carotene, XXVIII-3; β-carotene, XXVIII-4; γ-carotene, XXVIII-5). They suggest that fission at the central double bond is the likely mode of conversion to the vitamin. Since β-carotene has a symmetrical formula containing two β-ionone rings, one would expect oxidative cleavage to produce two molecules of vitamin A from this pigment. This is not borne out in animal experiments, one β-carotene molecule yielding only one molecule of vitamin A. At least two molecules of all the other provitamins are required for the

[2] Robeson and Baxter, *Nature*, **155,** 300 (1945); *J. Am. Chem. Soc.*, **69,** 136 (1947).

[2a] Fieser, *J. Org. Chem.*, **15,** 930 (1950).

[3] Kuhn and Morris, *Ber.*, **70,** 853 (1937). Karrer and Rüegger, *Helv. Chim. Acta*, **23,** 284 (1940). Isler, Huber, Ronco, and Kofler, *ibid.*, **30,** 1911 (1947). Isler *et al.*, *ibid.*, **32,** 489 (1949). Van Dorp and Arens, *Nature*, **160,** 189 (1947).



(XXVIII-1)

Figure 1[6] A Synthesis of Vitamin A

formation of one molecule of the vitamin, and it has therefore become necessary to interpret the conversion of the precursors to vitamin A as an asymmetrical fission.

[4] Van Dorp and Arens, *Rec. trav. chim.*, **65**, 338 (1946).
[5] Schwarzkopf, Cahnmann, Lewis, Sandinsky, and Wiest, *Helv. Chim. Acta*, **32**, 443 (1949).

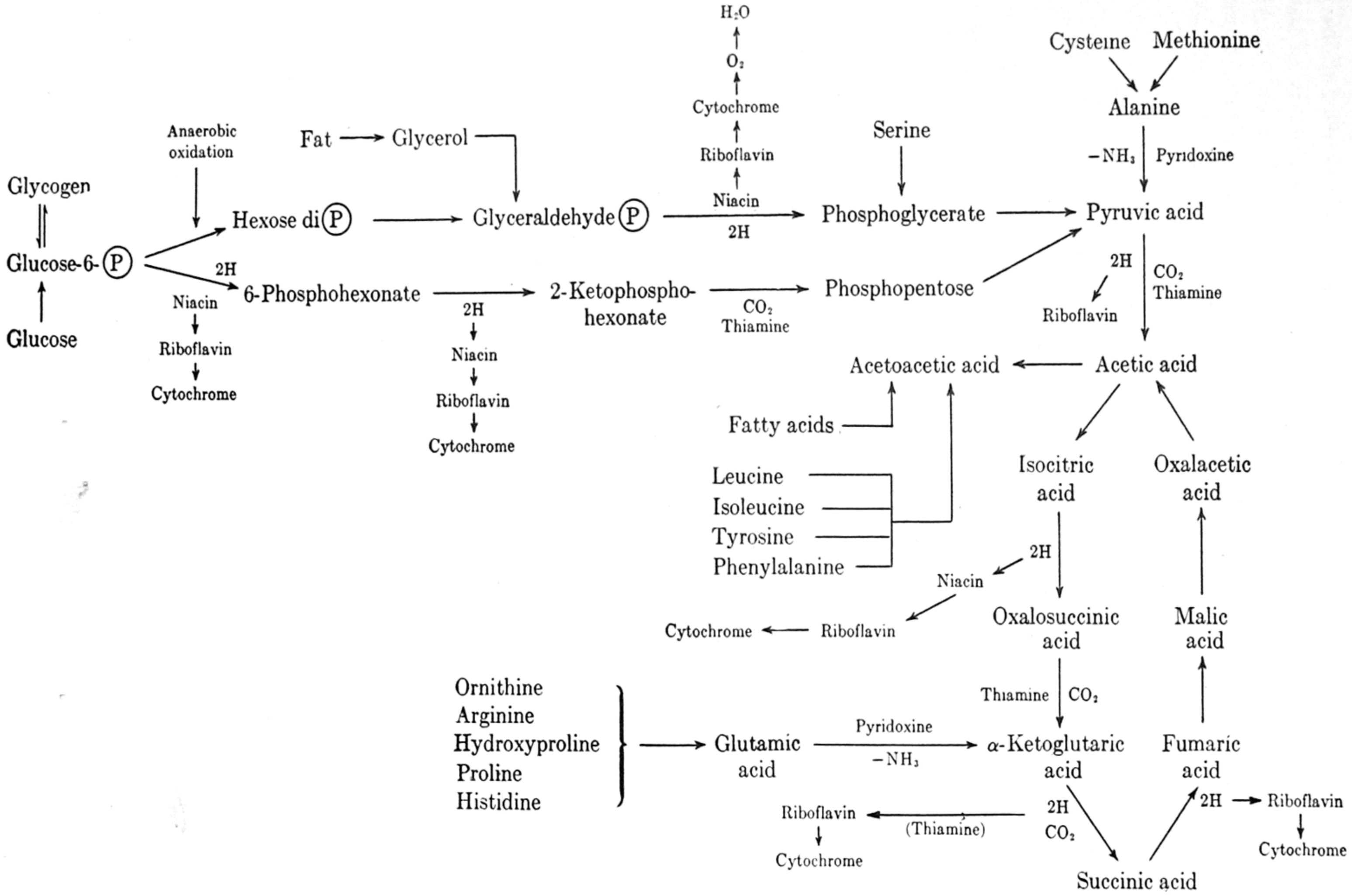


Figure 3. The B-Vitamins in Intermediary Metabolism

Not all of the B vitamins have been recognized as essential dietary constituents in man and in useful animals. However, further study of this question is needed to establish the exact physiological requirements. All these compounds are needed for multiplication and normal cellular functions of most microorganisms, and many tests for these vitamins are based on measurements of bacterial requirements.

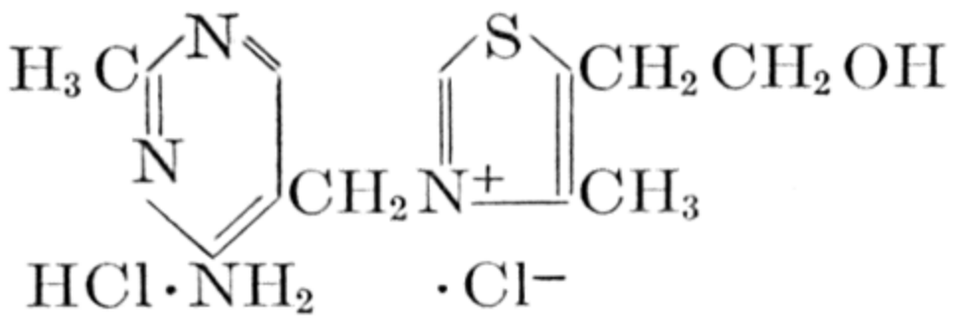
Vitamins B_1, B_2, B_{12}, niacin, pantothenic and pteroylglutamic acid have become important products of the pharmaceutical industry, and their correct medicinal application has contributed much to raise the health standards of large sections of the population.

The role of the members of the vitamin B complex in the biochemical cycles of glucose, protein and fat utilization has been represented in Figure 3. For details of the Krebs cycle, Figure 1 in Chapter V should be consulted.

a. Vitamin B_1—Thiamine

Vitamin B_1 (thiamine; foreign names, aneurin, oryzanine) occurs widely in the plant kingdom and is synthesized by bacteria and by higher plants for which it acts as a root growth hormone. Most green leaves contain about 75 γ per 100 grams, and higher concentrations are encountered in seeds, in the bran and in the germ. All animals require thiamine for the maintenance of the normal functions of their nervous system. Thiamine deficiency causes loss of appetite, fatigue and gastrointestinal disturbances; food intake is thereby reduced, and this in turn results in decreased synthesis and deposition of fatty acids. Advanced B_1-avitaminosis is known as polyneuritis and beriberi. It is caused by injuries to nerve tissues and leads to lameness, disturbances of the motor and sensory nerves, hypertrophy of the heart, and finally death from heart failure.

Severe cases of thiamine deficiency are still common in the Orient and are due to poor nourishment, the food consisting mainly of polished rice. Other causes of severe clinical B_1-hypovitaminosis are chronic alcoholism, poisoning by nicotine, lead, thallium, arsenic, beryllium, mercury etc., and general metabolic disorganization during pregnancy. Unless they are too far advanced, and too many organs have been affected degeneratively, all these cases yield to administration of food rich in thiamine, or better, to pure thiamine in adequate doses. This holds also for less pronounced deficiencies which are quite common and are caused by unwise choice of foods or destruction of thiamine by heat or alkali during cooking. In order to prevent wide-spread minor thiamine hypovitaminoses and their attendant nervous disorders, much of the bread, breakfast cereals and prepared foods are now enriched regularly with thiamine. For all these purposes, the vitamin is manufactured synthetically.



(XVIII-7)

The structural formula of thiamine (XXVIII-7) was elucidated about 15 years ago by the work of many investigators, notably, R. R. Williams and his coworkers.

Syntheses of thiamine are represented schematically in Figures 4 to 6.[7]

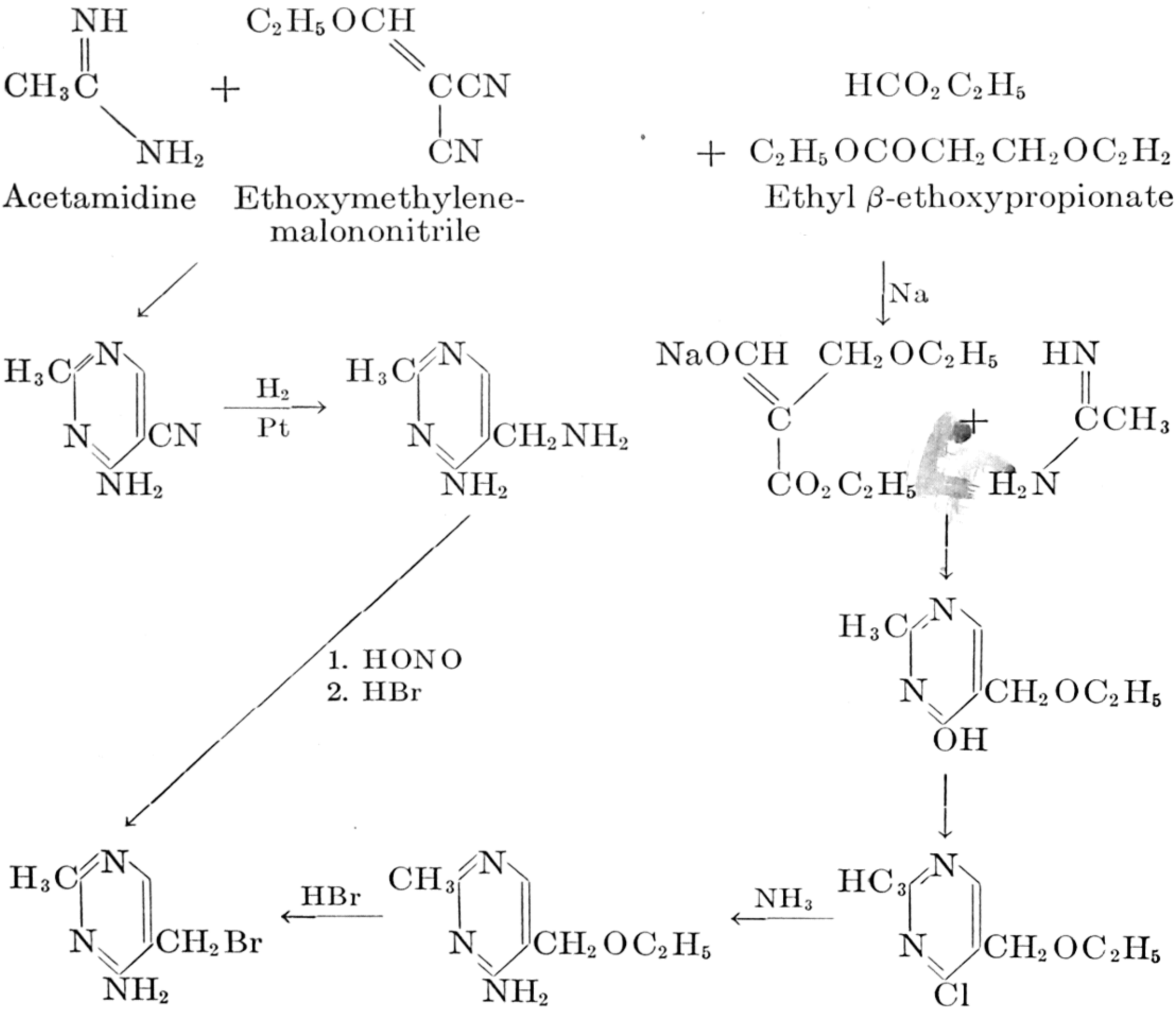


Figure 4. Synthesis of the Pyrimidine Moiety

[7] Williams and Cline, *J. Am. Chem. Soc.*, **58,** 1504 (1936). Cline, Williams, and Finkelstein, *ibid.*, **59,** 1052 (1937). Andersag and Westphal, *Ber.*, **70,** 2035 (1937). French Pat. 816,432. Matukawa and Ohta, U.S.Pat. 2,184,720.

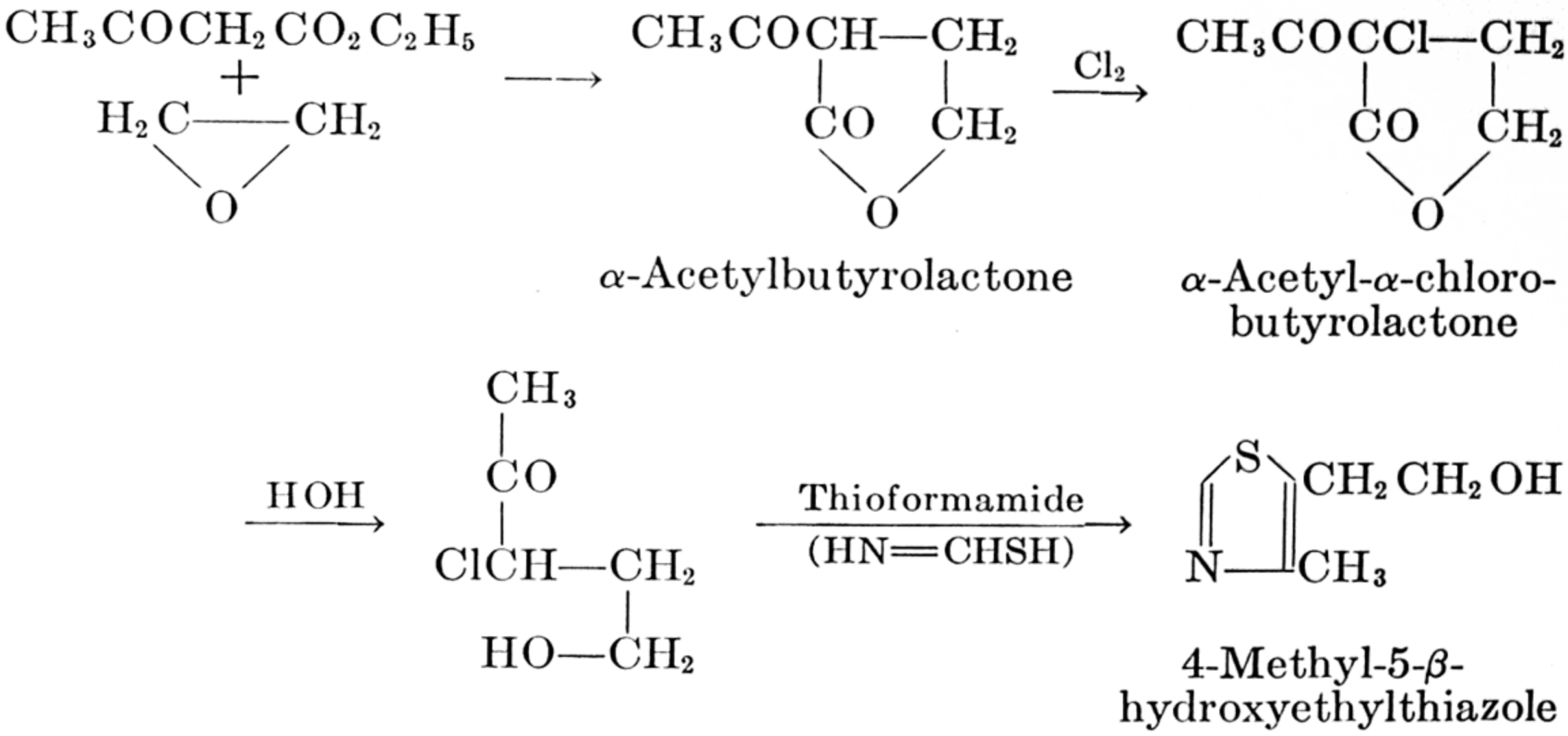
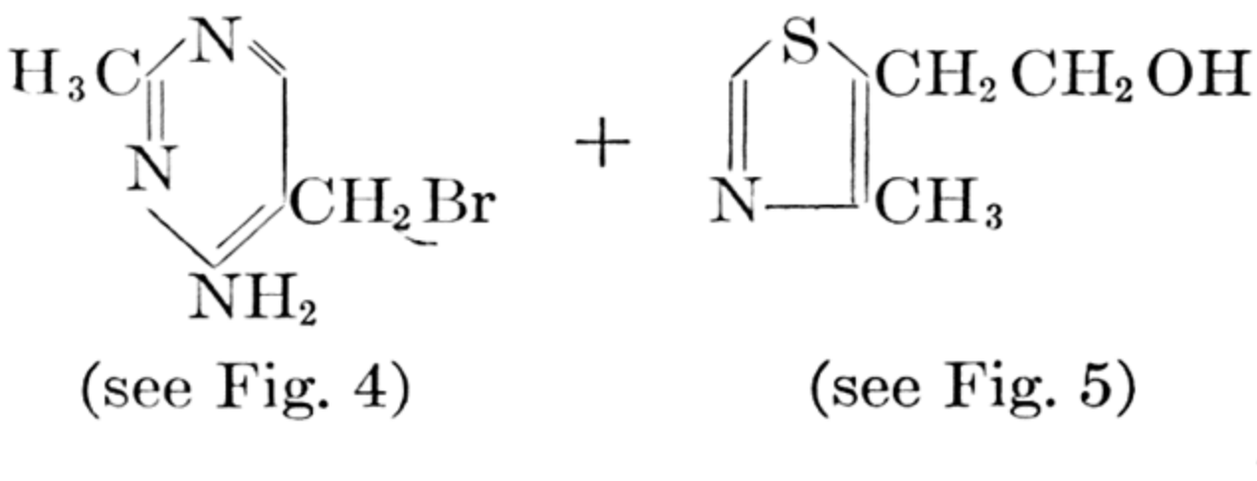


Figure 5. Synthesis of the Thiazole Moiety



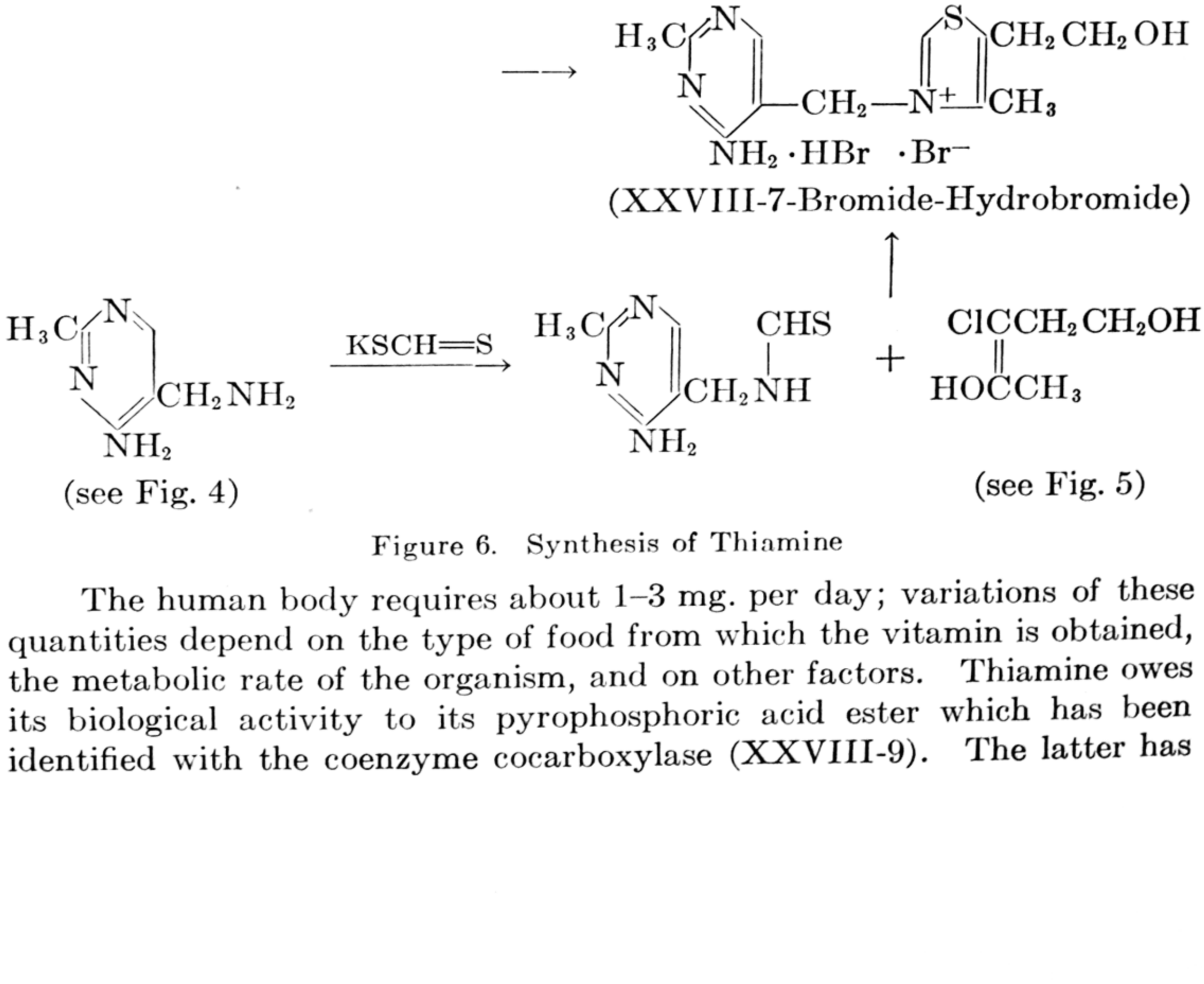
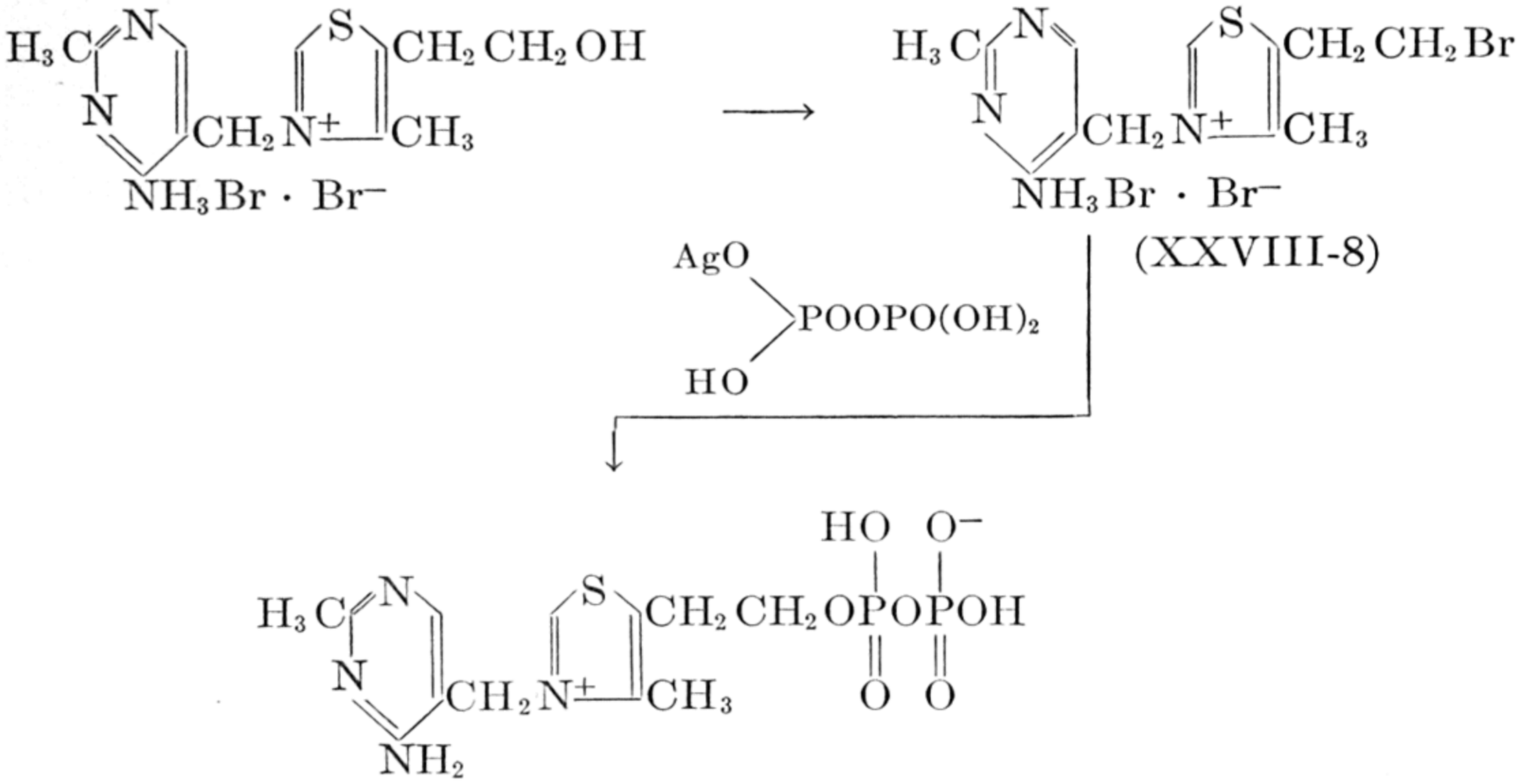


Figure 6. Synthesis of Thiamine

The human body requires about 1–3 mg. per day; variations of these quantities depend on the type of food from which the vitamin is obtained, the metabolic rate of the organism, and on other factors. Thiamine owes its biological activity to its pyrophosphoric acid ester which has been identified with the coenzyme cocarboxylase (XXVIII-9). The latter has

also been prepared synthetically from thiamine and salts or chlorides of pyrophosphoric acid, or by conversion of thiamine to the corresponding bromide (XXVIII-8) under the action of hydrobromic acid, and treatment of the bromide with silver pyrophosphate.



(XXVIII-8)

(XXVIII-9)

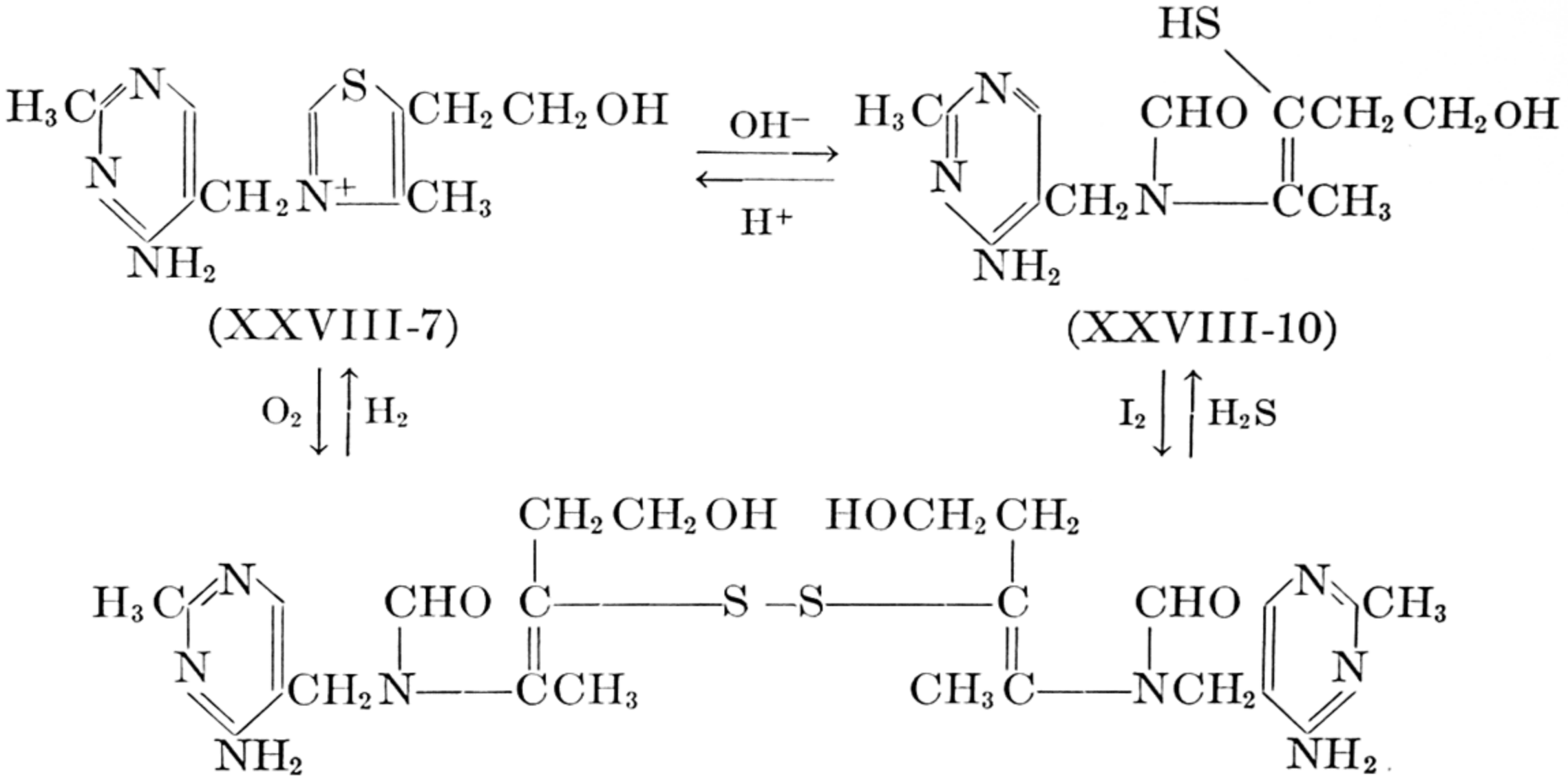
Cocarboxylase is part of the enzyme system carboxylase which consists of one molecular equivalent of a protein-type apoenzyme of molecular weight 150,000, one molecular equivalent of cocarboxylase, and 5 atoms of magnesium. Carboxylase occurs in yeast and many other cells, and is universally needed as a catalyst in carbohydrate metabolism. Acting through its coenzyme, it transfers phosphoric acid to and from other participants in the carbohydrate cycles (Chapter V), for example, adenosine triphosphate. The decarboxylation of pyruvic acid (a), and the carboxylation of pyruvic acid to oxalacetic acid (b) depend on the presence of cocarboxylase.

(a) $$CH_3COCOOH \rightarrow CH_3CHO + CO_2$$

(b) $$CH_3COCOOH + CO_2 \rightarrow HOOCCH_2COCOOH$$

Since both oxalacetic and pyruvic acid are key intermediates in the utilization of glucose, and in the interlacing of fat and protein degradation with glucose metabolism, B_1-hypovitaminosis will seriously interrupt the whole nutritional cycle. Peripheral and polyneuritis originate ultimately from the lack of energy-producing reactions of glucose and its metabolic products in nervous tissue.

The most important reactions in the biological utilization of glucose are dehydrogenations, and thiamine takes part in these oxidative steps. The vitamin represents the reduced form of a reversible oxidation-reduction system. A thiol form (XXVIII-10) of thiamine, in which the thiazole ring has been hydrogenolyzed, and a disulfide form (XXVIII-11) derived from it, participate in this redox system.



(XXVIII-11)

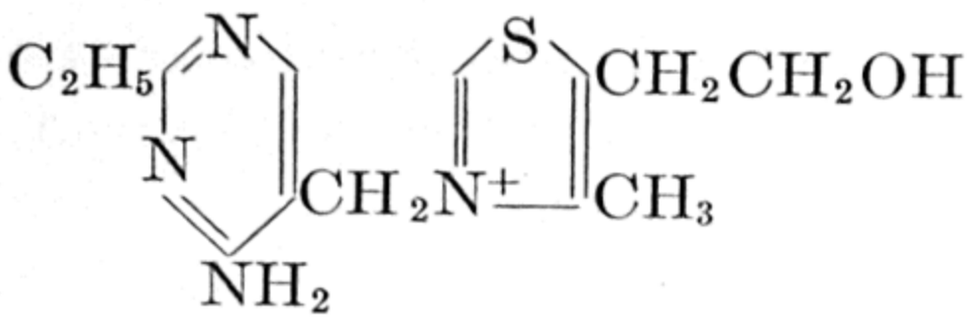
The disulfide (XXVIII-11) exhibits the same biological activity as thiamine and only about one-fifth the toxicity of the vitamin.

It is obvious, that the disulfide (XXVIII-11) may owe its activity to the ease with which it can be reduced to the vitamin. The pyrophosphate cocarboxylase is hydrolyzable to thiamine, and its activity can be explained on this basis. Any structural alteration abolishes activity, and this has led Williams to declare that thiamine activity is linked to a unique structure. Even such a minor alteration as substitution of hydroxyl for the 4-amino group in the pyrimidine nucleus leads to an inactive compound. To be sure, the 2-ethyl homolog of thiamine (XXVIII-12) can support growth of *Phyomyces*,[8] and in very large doses, an isomer of thiamine (XXVIII-13) has vitamin action.[9] But these two examples are not sufficient to detract from the uniqueness of the thiamine structure.

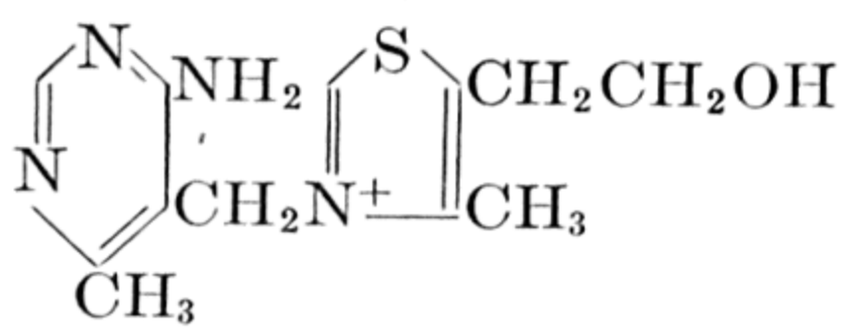
More profound alterations, such as the replacement of the thiazole by the isosteric pyridine ring, produce thiamine antagonists (see Neopyrithiamine, Chapter XXXII). This observation has stimulated considerable interest in the field of chemotherapy since antagonists of the bacterial

[8] Robbins and Kavanagh, *Proc. Natl. Acad. Sci. U. S.*, **24,** 229 (1938). *Compare,* Karrer, Schwyzer, and Kostic, *Helv. Chim. Acta,* **33,** 1482 (1950).

[9] Andersag and Westphal, *Ber.*, **70,** 2035 (1937).



(XXVIII-12)



(XXVIII-13)

growth promoting factor, thiamine, might conceivably have inhibitory effects on pathogenic organisms. This has been found to be so, but no useful drug has been evolved from this work.

b. Vitamin B_2—Riboflavin

(*1*) *Occurrence, Reactions and Functions*

Riboflavin (also called lactoflavin in Europe) occurs in all plants and animal cells. The best dietary sources are heart, liver, kidney, eggs, milk, yeast, green vegetables and germinated seeds. Because of its great importance for the normal functioning of the respiratory mechanism of body cells, it is routinely incorporated in enriched bread.

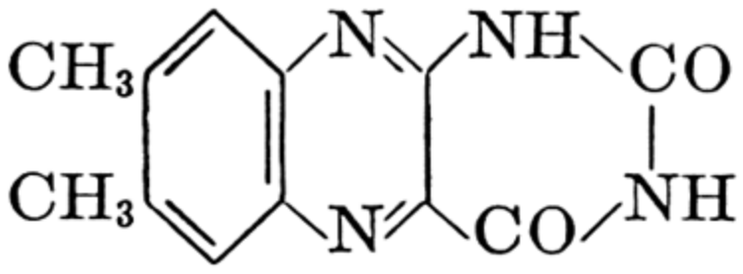
The vitamin occurs in the free state in places where little or no respiration or fermentation occurs, such as in milk, urine and the retina. Otherwise, riboflavin is encountered as phosphate ester, or combined with purine derivatives in the form of coenzyme molecules. The water soluble, orange-yellow crystalline vitamin can be purified by adsorption processes and can be separated from thiamine by its stability to autoclaving.

The riboflavin requirements in man are smaller than those of thiamine, but 2–3 mg. per day are usually given therapeutically. Deficiency of riboflavin in man leads to cheilosis, a cracking of the lips and corners of the mouth. The tongue is inflamed with a purplish or magenta color, the papillae are flattened (glossitis), the angles of the nose appear greasy, and ocular symptoms such as an itching sensation, photophobia, loss of dark adaptation, and opacity of the cornea may accompany ariboflavinosis. Similar deficiency symptoms are observed in animals, in addition to anemia, atrophy of the testicles, nervous degeneration, decreased egg production etc. in different species. All these symptoms are promptly improved or abolished by administration of riboflavin.

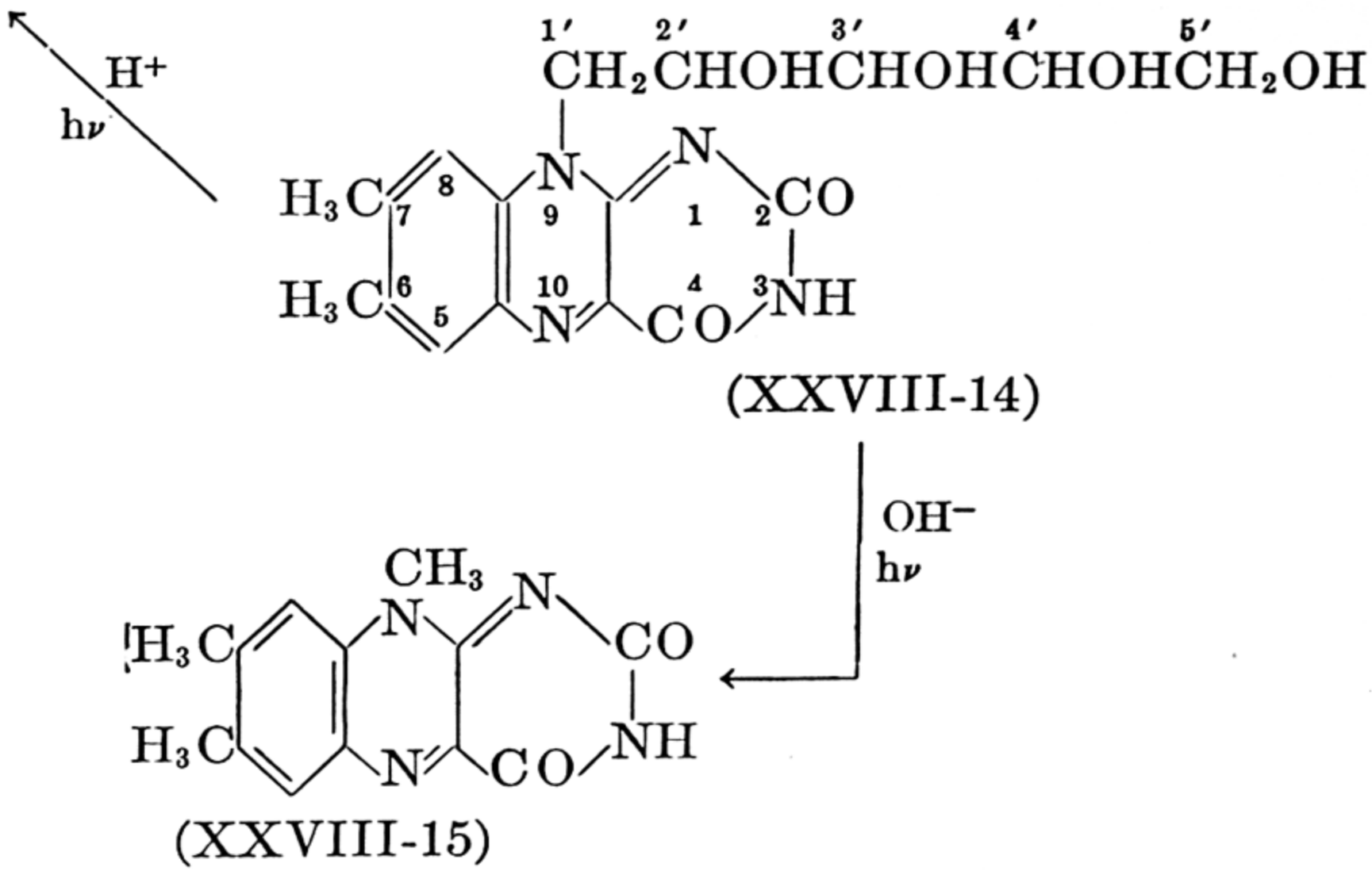
Riboflavin is 6,7-dimethyl-9-(1′-D-ribityl) isoalloxazine (XXVIII-14). Its structure and configuration was elucidated mainly by Kuhn and by Karrer and their associates. These groups of workers also accomplished the fundamental syntheses of the vitamin.

In the light, riboflavin rapidly loses its biological activity. The chemical changes accompanying this deactivation can be studied in different media. In alkaline solution, all but one carbon atom of the ribose chain are lost, and lumiflavin (6,7,9-trimethylisoalloxazine, XXVIII-15)

is formed. In neutral or acid solution, 6,7-dimethylalloxazine (lumichrome, XXVIII-16) is obtained; this is probably the mechanism of the normal deactivation of the vitamin by irradiation.



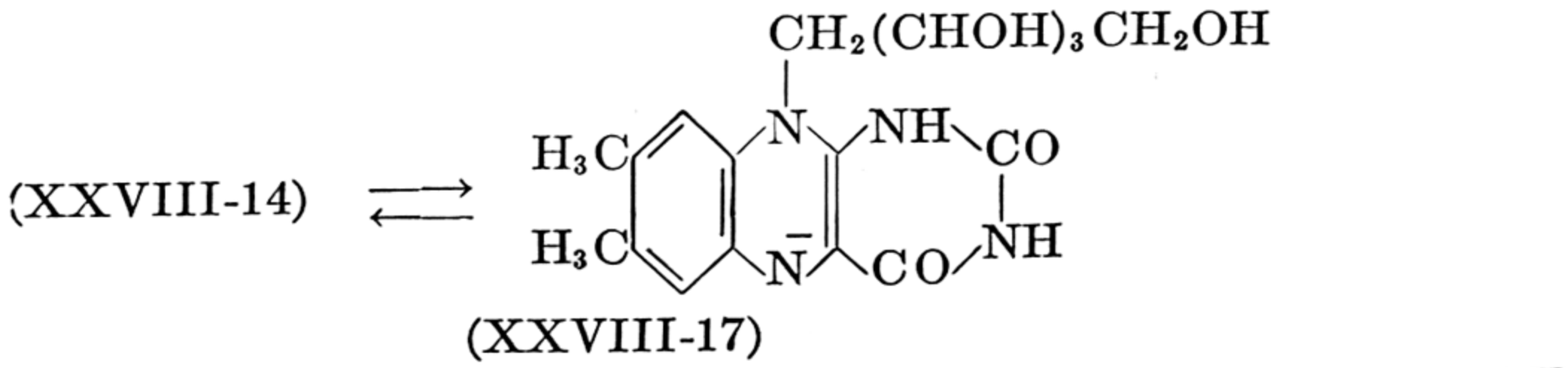
(XXVIII-16)



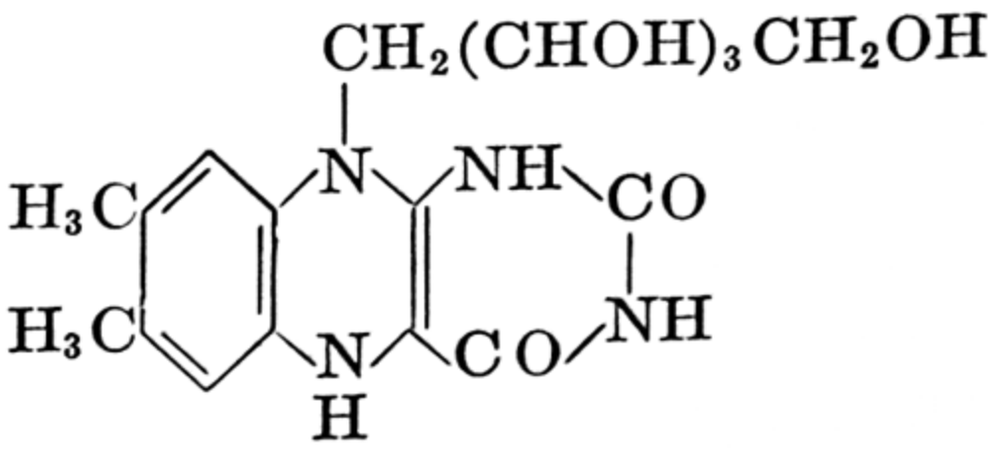
(XXVIII-14)

(XXVIII-15)

Riboflavin is an oxidation-reduction catalyst; hydrogenation proceeds by a 1,4-addition mechanism, a semiquinone stage (the green chloroflavin, XXVIII-17) being formed first. The latter is then reduced to the colorless leucoflavin (XXVIII-18). Dehydrogenation of leucoflavin goes through the same intermediate stage.

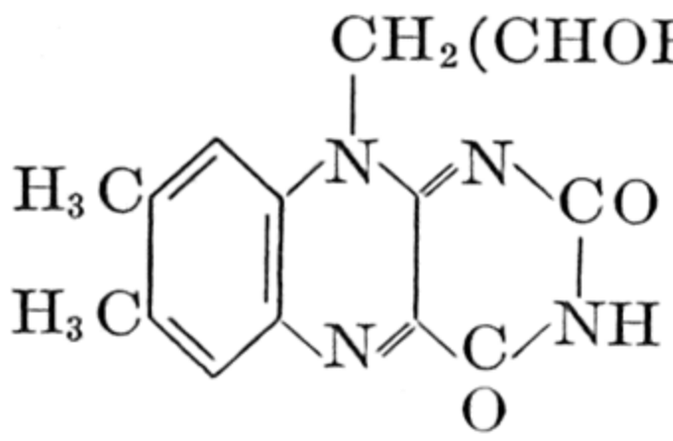


(XXVIII-17)

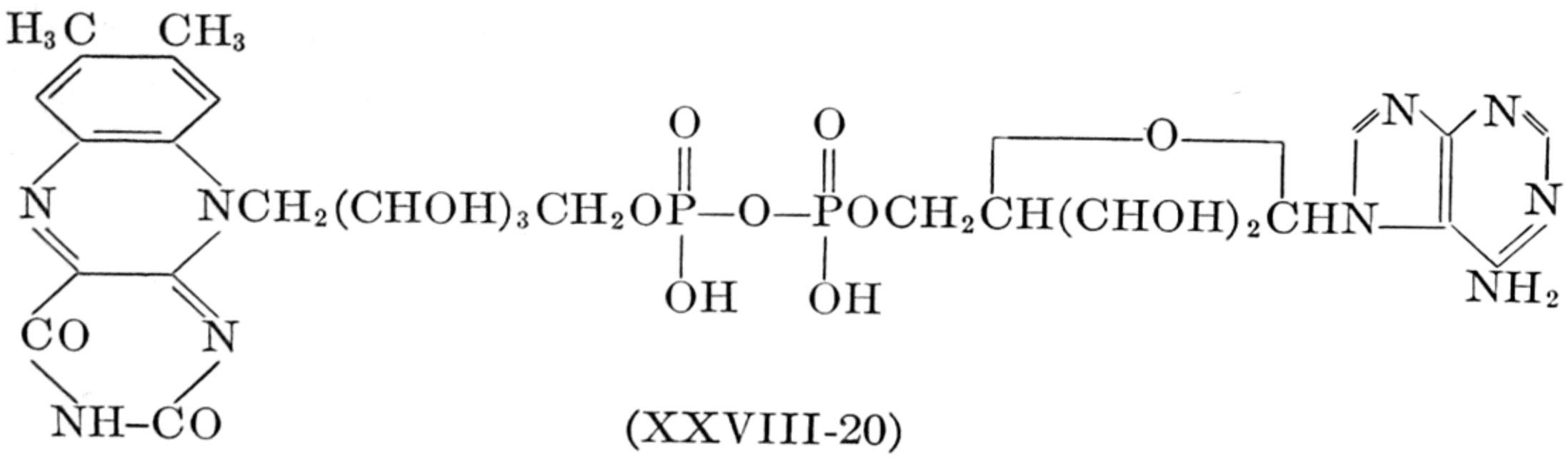


(XXVIII-18)

These reactions occur in nature not with riboflavin itself, but with riboflavin-5′-phosphoric acid (riboflavin mononucleotide; cytoflave; XXVIII-19) and riboflavin-5′-phosphoric acid-adenine-dinucleotide (XXVIII-20) which is riboflavin (adenosine-5′)-pyrophosphate.



(XXVIII-19)



(XXVIII-20)

The structure of the mononucleotide (XXVIII-19) has been confirmed by synthesis,[10] that of the dinucleotide by enzymatic and by acid hydrolysis. These nucleotides act as coenzymes; they are bound as prosthetic groups to proteins in important enzyme systems such as the yellow enzyme of respiration, cytochrome C reductase, xanthine oxidase, D-amino acid oxidase, diamine oxidase, and others. The function of these enzymes is hydrogen transfer, and they catalyze mainly reversible dehydrogenations between the niacin-containing coenzymes I and II and the iron-porphyrine type cytochromes.

Another relation exists between riboflavin and the steroid hormones of the adrenal cortex. The latter transmit phosphoric acid to riboflavin. The actions of insulin and thyroxine are also interlocked with that of riboflavin.

(2) *Manufacture of Riboflavin*

Riboflavin is now manufactured by two different routes. Large amounts are needed for animal feeds since the quality of the milk of cattle, and the

[10] Kuhn, Rudy, and Weygand, *Ber.*, **69,** 1543 (1936). Kuhn and Rudy, *ibid.*, **69,** 1974 (1936). Kuhn and Rudy, *ibid.*, **69,** 2557 (1936). Abraham, *Biochem. J.*, **33,** 543 (1939).

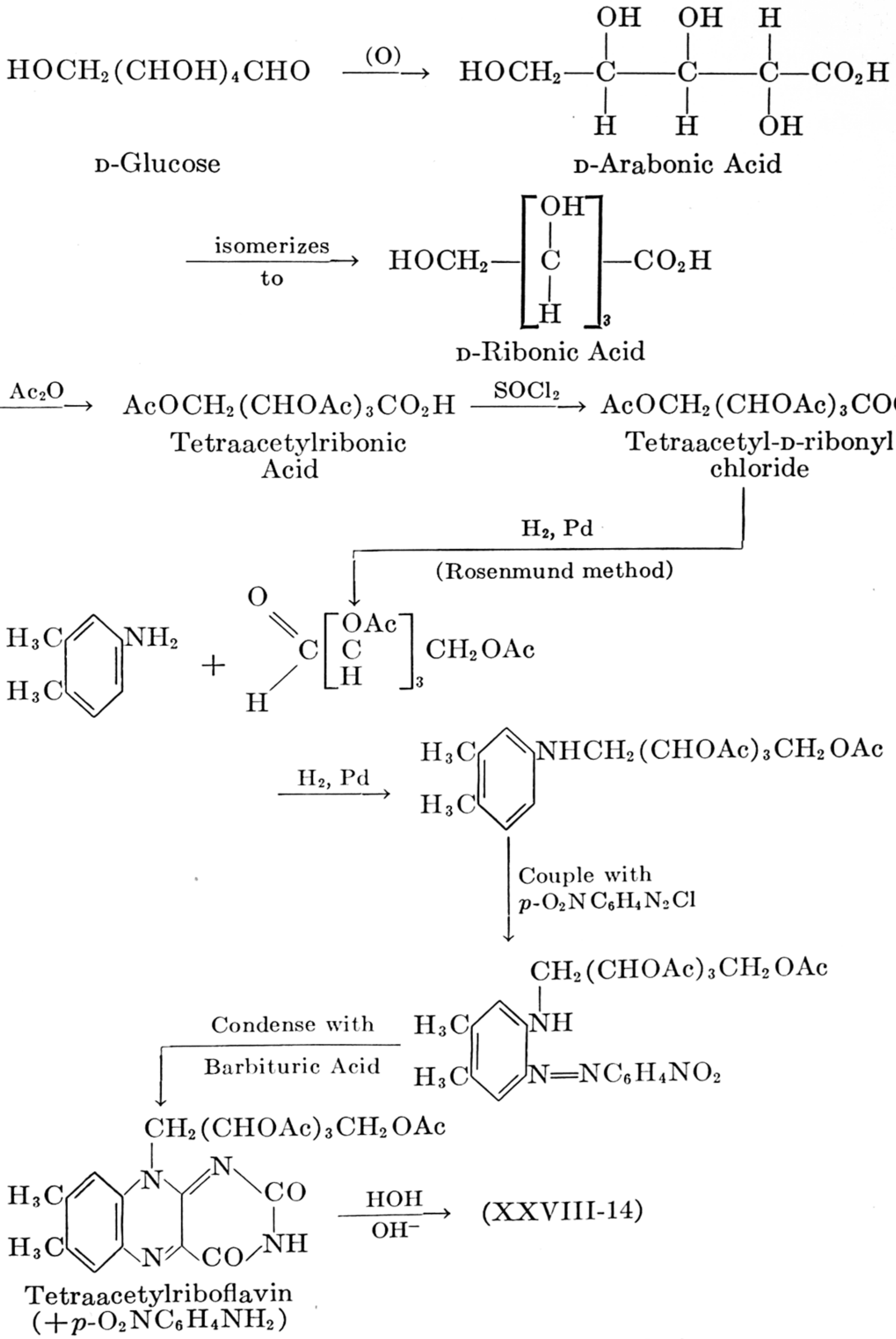


Fig. 7. A Commercial Synthesis of Riboflavin

laying ability of fowl are dependent on a proper riboflavin-containing diet. Here, where highest purity is not required, vitamin concentrates are used which are obtained from yeast, from bacterial growth on whey, and from the residues of anaerobic butanol fermentations.

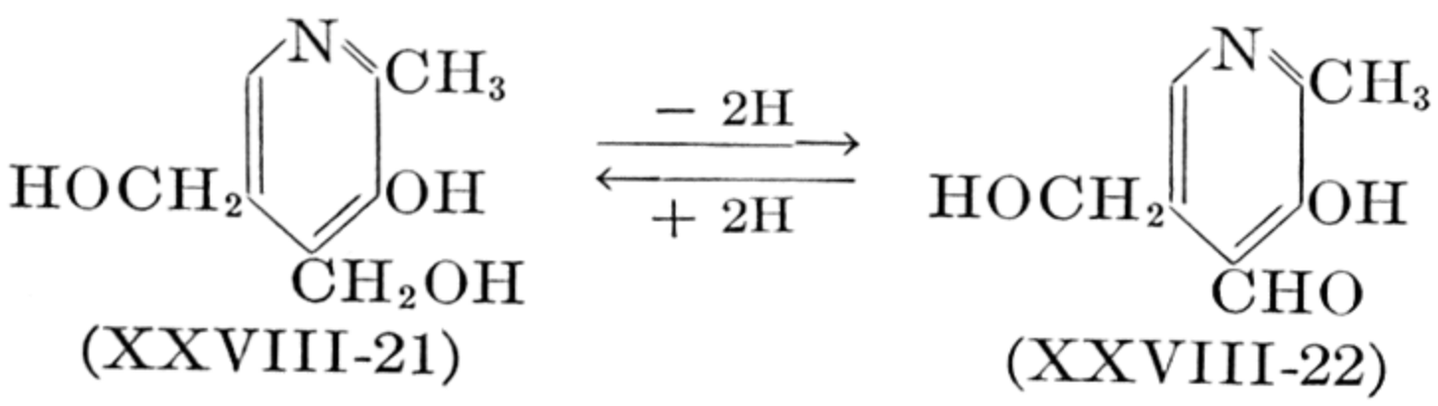
Of the several commercial syntheses of pure riboflavin, only one is presented in Figure 7 in schematic form. Several of its main steps have been suggested by the earlier syntheses of Kuhn and of Karrer. The main innovations lie in the utilization of barbituric acid in place of the expensive alloxan in building up the isoalloxazine ring system, and in simplifications of the manufacture of tetraacetyl ribose from glucose.[11]

(3) *Analogs of Riboflavin*[12]

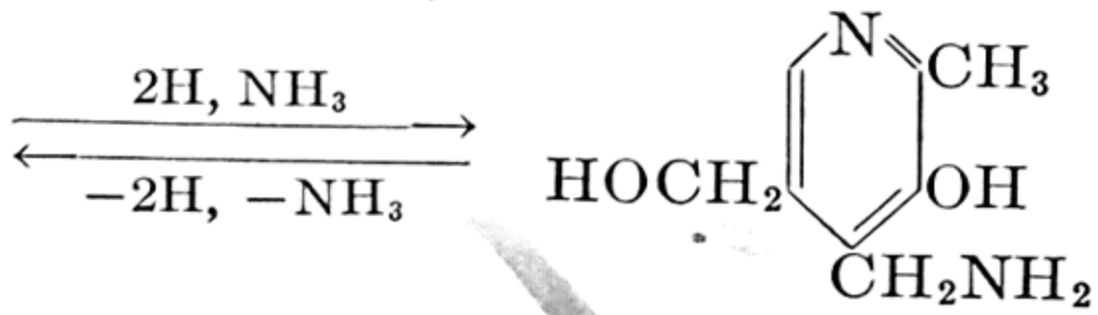
Three synthetic homologs of riboflavin exhibit, in rats, about one-half the vitamin activity of their naturally occurring prototype. They are 7-methyl-, 6-methyl-, and 6-ethyl-7-methyl-9-(D-1′-ribityl)-isoalloxazines. A low degree of stimulating activity is observed in the L- or D-arabityl analogs of the vitamin, the 6,7-trimethylene- and 6,7-tetramethylene-9-L-arabityl analogs, and the 7-ethyl analog of riboflavin. Substitution in the 6- or 7-positions with small alkyl groups seems to be prerequisite for vitamin activity. The unsubstituted ribityl-isoalloxazine derivative is highly toxic, and substitution by two chlorine atoms in positions 6 and 7 leads to a compound with antagonistic properties (Chapter XXXII). Replacement of the imino hydrogen in position 3 by alkyl groups produces completely inactive derivatives.

c. Vitamin B_6

Vitamin B_6 has been found in many plant and animal cells where it occurs to a great extent as a protein or starch complex. It appears in



(XXVIII-21) (XXVIII-22)



(XXVIII-23)

[11] Tishler, Pfister, Babson, Ladenburg and Fleming, *J. Am. Chem. Soc.*, **69,** 1487 (1947). Tishler and Wellman, U. S. Pat. 2,261,608.

[12] Rosenberg, *Chemistry and Physiology of the Vitamins*. Interscience, New York, 1942, p. 181.

three forms, the best-known of which is the glycol, pyridoxine (XXVIII-21). The other two are the corresponding aldehyde, pyridoxal (XXVIII-22) and the amine, pyridoxamine (XXVIII-23). These three compounds can be converted into each other in metabolic processes. Phosphorylated pyridoxal acquires reductively one molecule of ammonia to yield phosphorylated pyridoxamine, and the reverse reaction, oxidative deamination, liberates one mole of ammonia. The latter is transferred to proteinogenous keto acids which are thereby converted to amino acids for protein synthesis. This "transamination reaction" is reversible. Ordinarily, glycine furnishes amino groups to keto acids and is thereby converted to glyoxylic acid. Pyridoxine protects rats from the toxic effects of massive doses of glycine, that is, from doses too large to be transaminated without the aid of the coenzyme.

$$RCOCO_2H \underset{\text{pyridoxamine, 2(H)}}{\overset{NH_3 \text{ from}}{\rightleftharpoons}} RCH(NH_2)CO_2H + H_2O$$

Pyridoxal phosphate and pyridoxamine also serve as coenzymes in the enzymatic decarboxylation of proteinogenous amino acids, and thus are essential for protein catabolism and anabolism.

The early work on this group of vitamins centered principally on pyridoxine, and the drug industry manufactures this compound for therapeutic administration by synthetic methods worked out by Kuhn, and by Folkers and Harris and their collaborators.[13] These syntheses either build up the pyridine ring, or provide it by degradative reactions of isoquinoline derivatives. They are schematized in Figure 8.

Like other B-vitamins, pyridoxine is needed as a metabolite by many microorganisms. If not supplied by their surroundings, the bacteria often synthesize their own needs. Ruminant animals which have a bacterial flora living in the rumen draw upon these symbiotic organisms as a source of vitamin B_6. Deficiency in certain domestic animals leads to spasms, convulsions and a specific dermatitis. It is possible that man also can obtain pyridoxine from his intestinal flora. However, clinical use is made of doses up to 2 mg. per day to counteract insomnia, vertigo, nervousness, morning sickness in pregnancy etc. Vitamin B_6 is incorporated in certain multiple vitamin tablets as an adjunct in the therapy of pellagra, and as a prophylactic of general health.

[13] Harris and Folkers, *J. Am. Chem. Soc.*, **61,** 1245 (1939). Harris, Stiller, and Folkers, *ibid.*, **61,** 3307 (1939). Kuhn, Westphal, Wendt, and Westphal, *Naturwissenschaften*, **27,** 469 (1939). Itiba and Miti, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), **36,** 173 (1939).

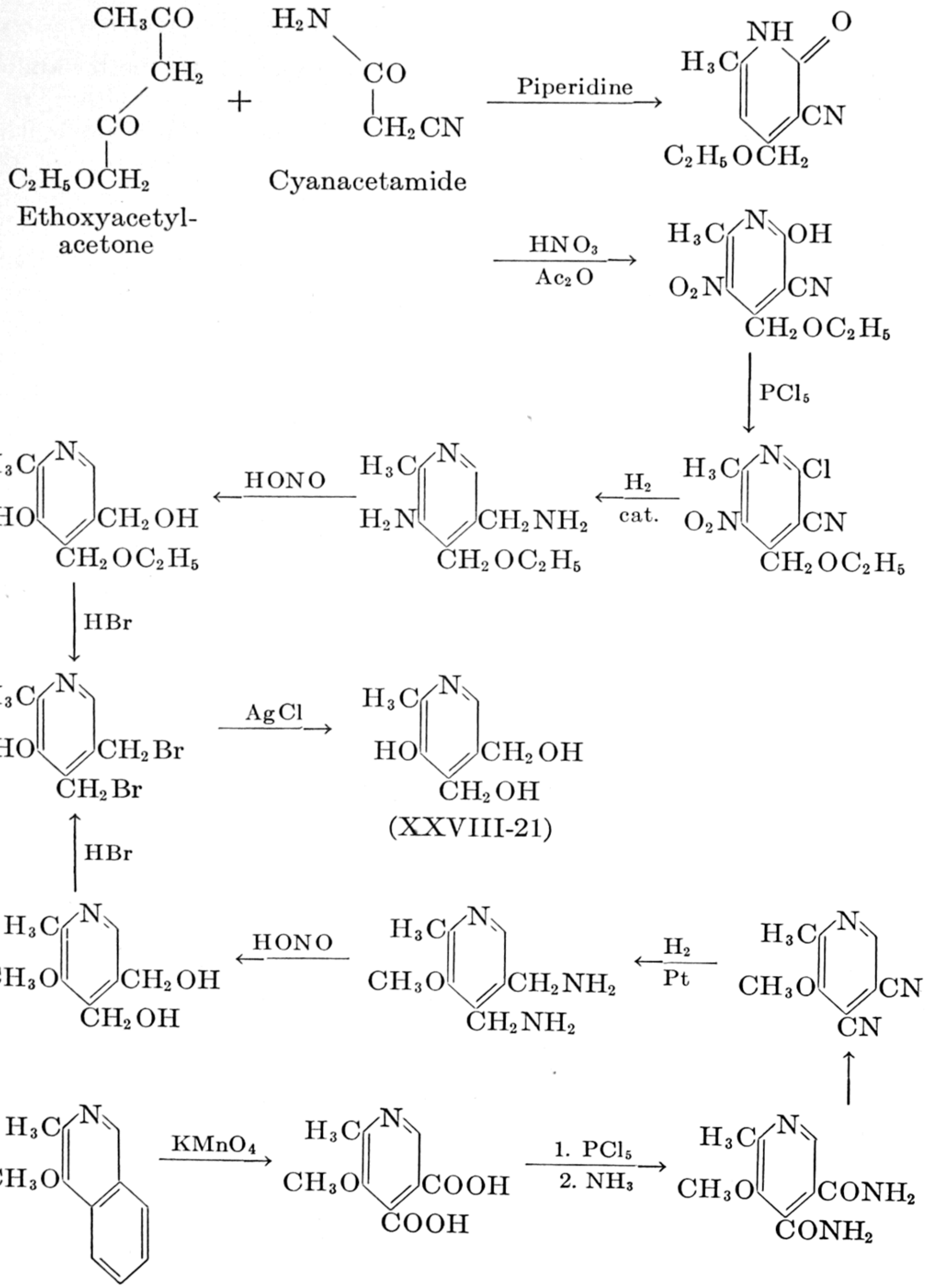
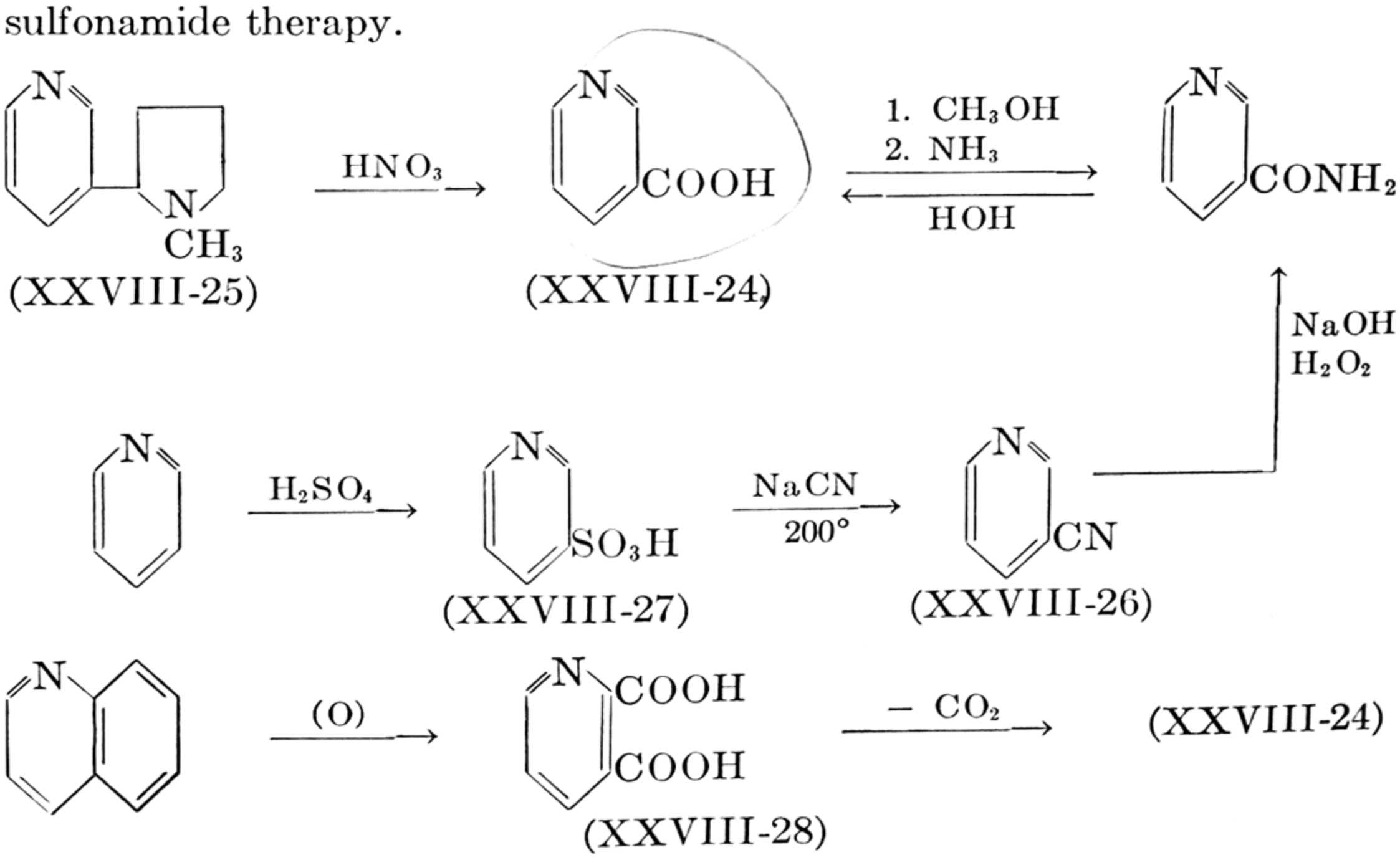


Figure 8. Syntheses of Pyridoxine

d. Niacin and Niacinamide

Niacin and niacinamide are N. N. R. synonyms for the better-known older names, nicotinic acid and nicotinamide, respectively. Other, now abandoned names include pellagramine, niamid and pellagra-preventive (P. P.) factor. The last name indicates the medicinal function of the vitamins. Pellagra is a niacin deficiency which produces characteristic lesions of mucous membranes and of the skin in various parts of the body, especially those which are exposed to sunlight or to friction. In addition, gastrointestinal disturbances and in advanced stages of the disease, mental disorders and insanity are observed. However, pellagra is caused more often by a multiple vitamin deficiency and also exhibits symptoms which respond to thiamine and riboflavin therapy. In animals, the blacktongue of dogs is directly due to niacin deficiency, and can be cured by administration of the vitamin.

Niacinamide is the preferred therapeutic agent since it is tolerated better than the free acid, niacin; the body has the ability to convert niacin to its amide if the former is used. The vitamin is administered in daily doses of 50 to 500 mg. for the treatment of various stages of the pellagra syndrome, and for overcoming certain toxicity symptoms incurred during sulfonamide therapy.

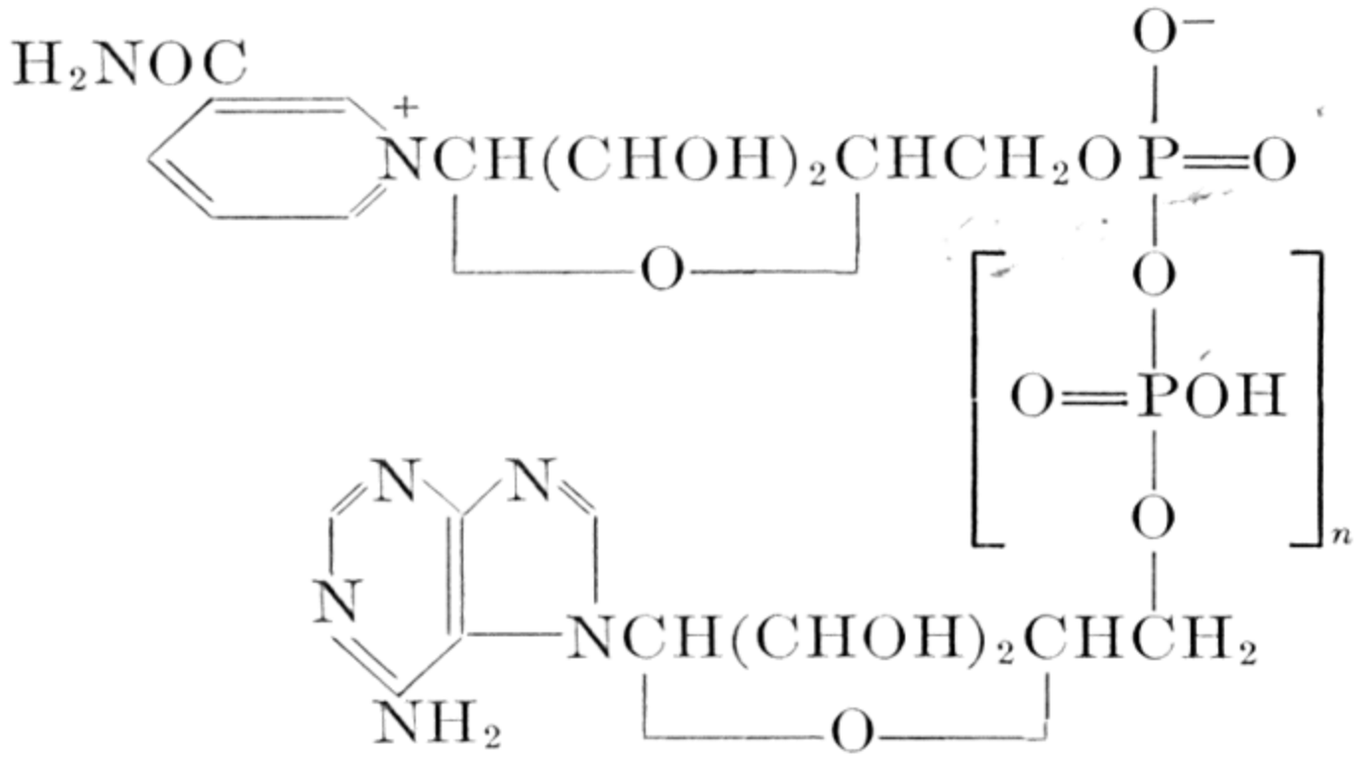


(XXVIII-25) (XXVIII-24) (XXVIII-27) (XXVIII-26) (XXVIII-28) (XXVIII-24)

Nicotinic acid (XXVIII-24) derived its name from the fact that it was first obtained by nitric acid oxidation of the tobacco alkaloid nicotine (XXVIII-25). This mode of preparation which results in a destruction of the pyrrolidine ring of nicotine, was used in the early years of the manu-

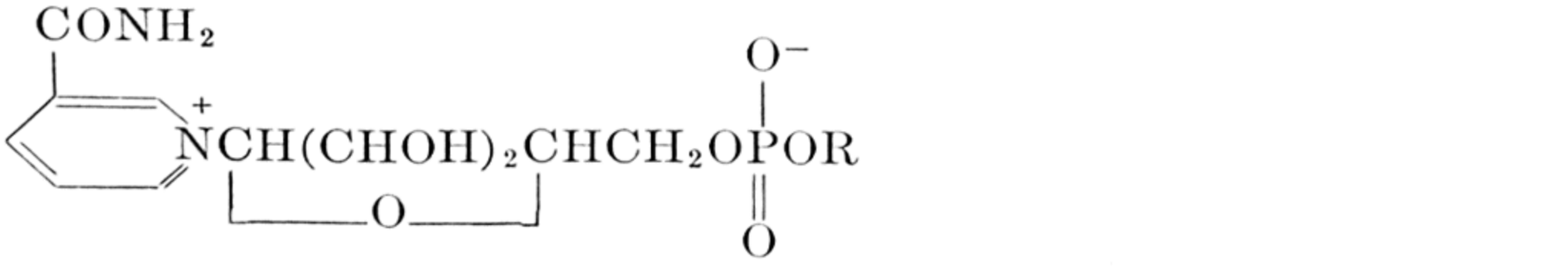
facture of niacin after its vitamin nature had been recognized (1936–1942). Since then, two commercial methods have superseded most others. They are the preparation of 3-cyanopyridine (XXVIII-26) *via* the sulfonic acid (XXVIII-27), followed by partial hydrolysis to the amide, or complete hydrolysis to niacin, and the oxidation of quinoline to quinolinic acid (XXVIII-28) followed by decarboxylation in the α-position.

The mechanism of biological action of niacinamide is understood best if its most common naturally occurring combinations are studied. Free niacinamide is found widely in many cells, but all living cells which metabolize carbohydrates contain small amounts of two coenzymes which in turn owe their activity to the niacinamide moiety in their molecules. The coenzymes are called codehydrogenase I or cozymase, and codehydrogenase II. They consist of a niacinamide group, linked by way of a quaternary nitrogen linkage to D-ribose which is esterified with adenosine diphosphate in codehydrogenase I (XXVIII-29), and with adenosine triphosphate in codehydrogenase II (XXVIII-30).

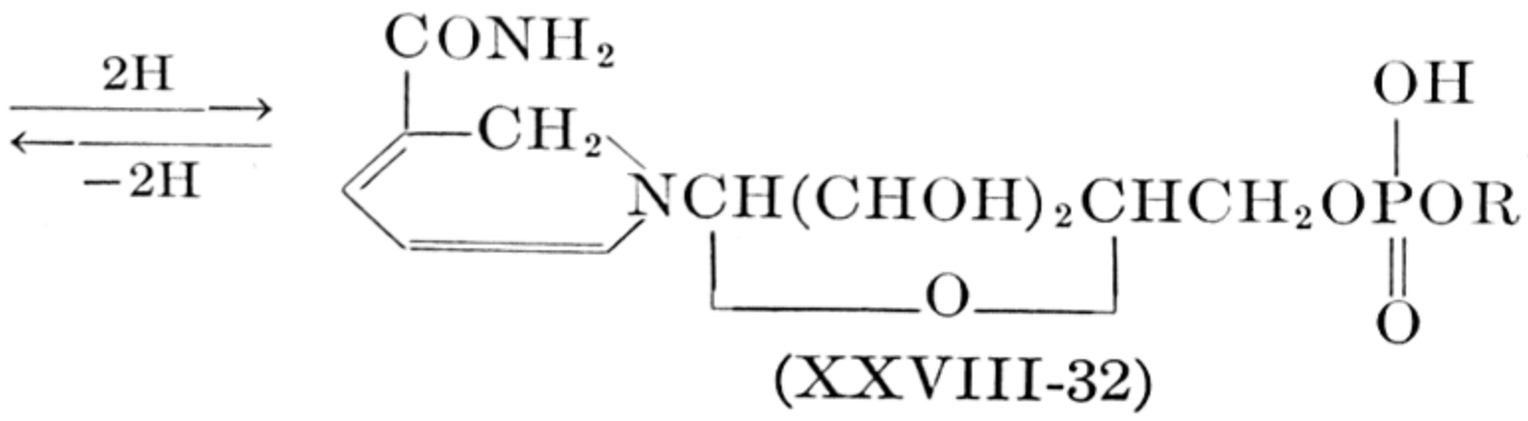


$n = 1$ (XXVIII-29)
$n = 2$ (XXVIII-30)

These coenzymes participate in many of the reversible oxidation steps of the glucose utilization cycles and serve as hydrogen acceptors by being



(XXVIII-31)

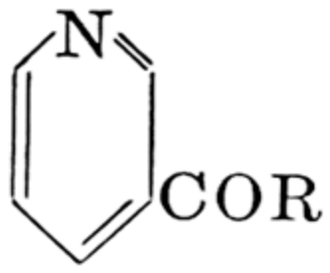


(XXVIII-32)

reduced at the 1,2-positions of the pyridine ring. This converts the quaternary pyridinium compounds (XXVIII-31) to tertiary 1,2-dihydropyridine derivatives (XXVIII-32).

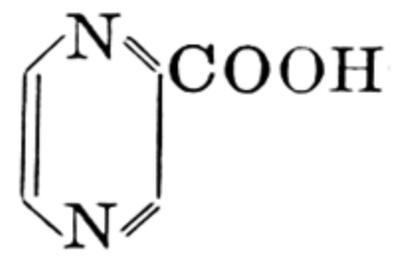
Both cozymase and codehydrogenase II have been synthesized. The reason for differences in the catalytic ability of the two coenzymes is not understood.

Weak vitamin activity is exhibited by a few derivatives of niacin which can conceivably be hydrolyzed to the parent acid in the body. They are, ethyl nicotinate (XXVIII-33), N-methylnicotinamide (XXVIII-34), N,N-diethylnicotinamide (Coramine, XXVIII-35) and nicotinuric acid (XXVIII-36).

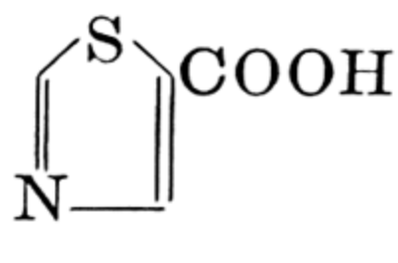


R =	OC_2H_5	(XXVIII-33)
	$NHCH_3$	(XXVIII-34)
	$N(C_2H_5)_2$	(XXVIII-35)
	$NHCH_2COOH$	(XXVIII-36)

Quinolinic acid (XXVIII-28) is also active and has been used clinically. It undoubtedly owes its activity to its *in vivo* decarboxylation to niacin. Several isosteres of niacin exhibit weak activity, particularly pyrazine carboxylic acid (XXVIII-37), and thiazole-5-carboxylic acid (XXVIII-38). Their activity is observed best when they are used as growth factors for microorganisms.



(XXVIII-37)



(XXVIII-38)

e. Panthothenic Acid

Like some of the other members of the vitamin B complex, pantothenic acid (Pantothen) occurs universally in animal cells, mainly bound to protein. Although it is undoubtedly an essential metabolic factor, no deficiency symptoms in the absence of pantothenic acid from the diet have been observed in man. This may be due to the fact that intestinal bacteria can synthesize the vitamin for their own needs, and incidentally provide their host's requirements. In animals, pantothenic acid deficiency is known; the hatchability of hens eggs is reduced, the fur of many mammals turns gray, and growth and reproduction are impaired.

These symptoms are overcome by administration of pantothenic acid with the diet. The vitamin is marketed largely as calcium pantothenate, and is incorporated into vitamin B-complex preparations in this form as a prophylactic agent against general B-hypovitaminoses.

Pantothenic acid is normally obtained from egg yolk, liver, yeast, fish, milk, beef and a number of vegetable products. It was isolated from liver and purified by R. J. Williams and his associates[14] who also elucidated the structure of the compound as (2,4-dihydroxy-3,3-dimethylbutyryl)-β-alanine (XXVIII-39). The synthesis of the compound was accomplished in three laboratories in 1940.[15] It is schematized in Figure 9.

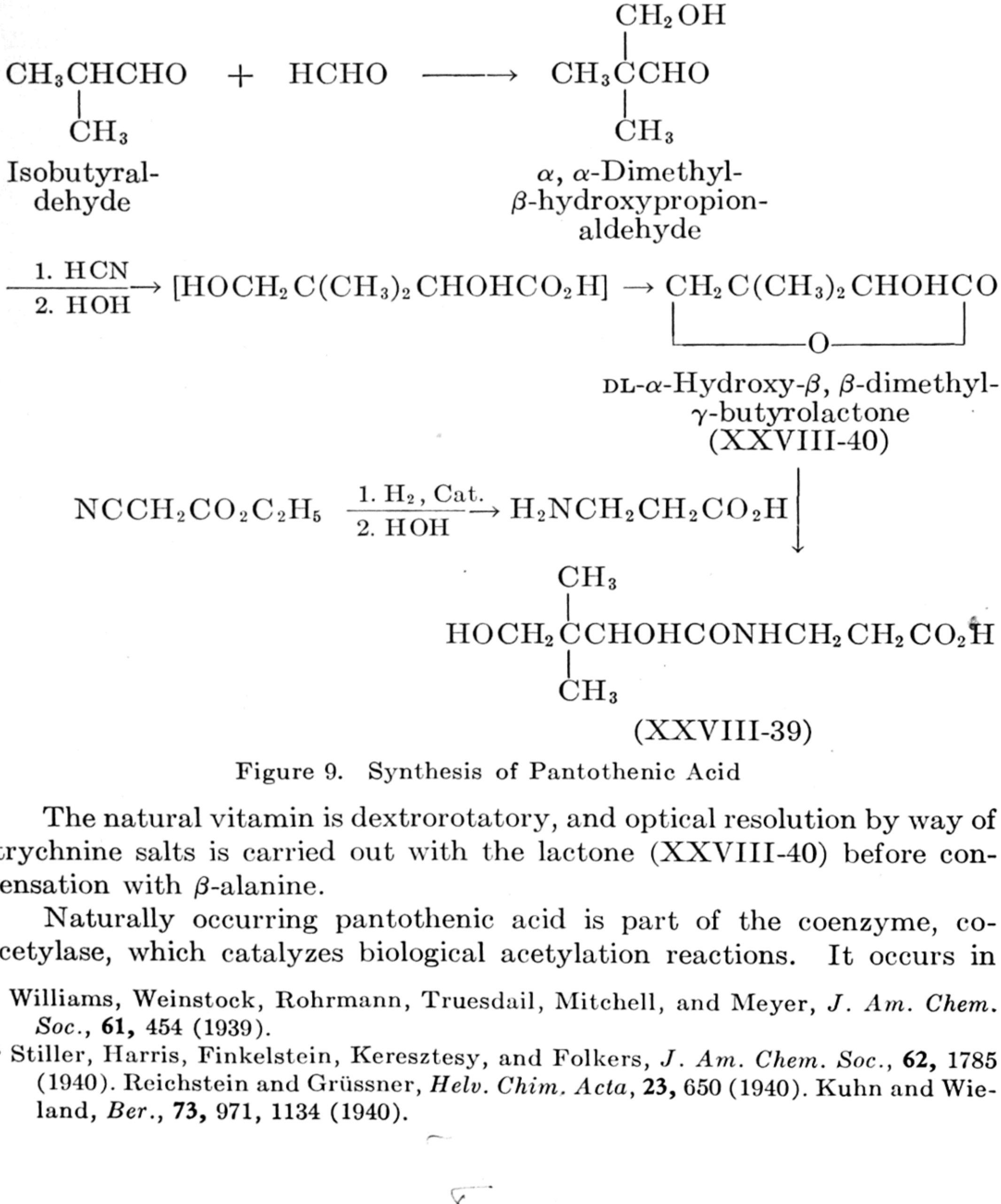


Figure 9. Synthesis of Pantothenic Acid

The natural vitamin is dextrorotatory, and optical resolution by way of strychnine salts is carried out with the lactone (XXVIII-40) before condensation with β-alanine.

Naturally occurring pantothenic acid is part of the coenzyme, coacetylase, which catalyzes biological acetylation reactions. It occurs in

[14] Williams, Weinstock, Rohrmann, Truesdail, Mitchell, and Meyer, *J. Am. Chem. Soc.*, **61,** 454 (1939).

[15] Stiller, Harris, Finkelstein, Keresztesy, and Folkers, *J. Am. Chem. Soc.*, **62,** 1785 (1940). Reichstein and Grüssner, *Helv. Chim. Acta*, **23,** 650 (1940). Kuhn and Wieland, *Ber.*, **73,** 971, 1134 (1940).

coacetylase as a nucleotide containing adenylic acid.[16] The structure of pantothenic acid is highly specific, and small and often insignificant changes abolish vitamin activity. Not even all compounds which could be converted to pantothenic acid *in vivo* are active; thus, the acetate, benzoate and pyrophosphate esters of the primary alcohol function are inactive. Esterification of the carboxyl group in the β-alanine moiety retains activity.

A number of synthetic analogs of pantothenic acid obtained by condensation of various hydroxylactones with β-alanine possess less than 1% of the activity of the vitamin. Some of their formulas are given below.

$CH_3CHOHCH_2CHOHCONHCH_2CH_2COOH$

$HOCH_2CH(CH_3)CHOHCONHCH_2CH_2COOH$

$HOCH_2CH_2C(OH)(CH_3)CONHCH_2CH_2COOH$

$HOCH_2CHOHCHOHCONHCH_2CH_2COOH$

$HO(CH_2)_3CHOHCONHCH_2CH_2COOH$

$HOCH_2CH_2CHOHCONHCH_2CH_2COOH$

$HO(CH_2)_4CHOHCONHCH_2CH_2COOH$

$(HOCH_2)_2C(CH_3)CHOHCONHCH_2CH_2COOH$

(XXVIII-41)

Only one such compound, the so-called hydroxypantothenic acid (XXVIII-41) has as much as one-fourth of the growth-promoting ability of pantothenic acid for various microorganisms.

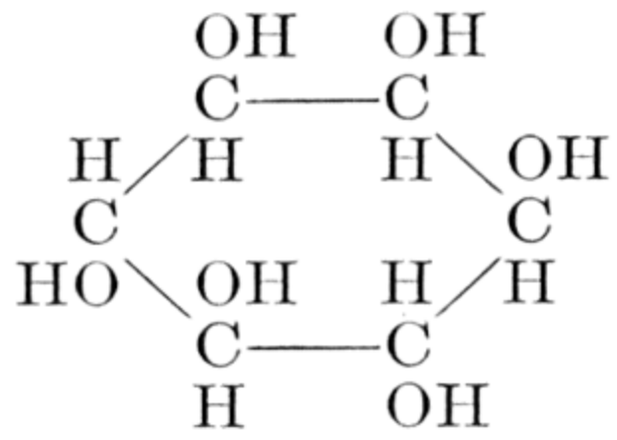
Some organisms can convert β-alanine to pantothenic acid and depend on an external supply of the β-amino acid for their needs. Others can supply the β-alanine portion but not dihydroxy-dimethylbutyric acid. Substitution of structurally related compounds for these prerequisite units have led to inhibition of culture growth. Other antagonists to pantothenic acid are described in Chapter XXXII.

f. Inositol

Almost all plant and animal tissues contain the cyclic carbohydrate, *meso*-inositol (XXVIII-42) either in the free state, as an alkali-labile protein complex, in the form of phytin (a Ca-Mg derivative in plants), or as a glycoside of a phosphatide fraction. Several beans, seeds and citrus fruits provide adequate nutritional sources of the compound.

[16] Lipmann, Kaplan, Novelli, Tuttle, and Guirard, *J. Biol. Chem.*, **167,** 869 (1947).

Like other carbohydrates, inositol is phosphorylated before being utilized. Inositol phosphate forms part of the molecule of pancreatic amylase which catalyzes the hydrolysis of polysaccharides in the duodenum.



(XXVIII-42)

This is probably the way the animal or human body utilizes the compound. No specific avitaminosis in man has been observed, and inositol is therefore not a common ingredient of multiple vitamin medication. Inositol deficiency in laboratory animals is expressed by dermatitis and other symptoms resembling other B-avitaminoses.

g. Biotin

Biotin, formerly called vitamin H, is a vitamin which combines stoichiometrically with the protein avidin from egg white and can then not be absorbed through the intestinal wall. Consequently, it appeared to early students of this "bios" factor that egg white was injurious to laboratory animals and withheld from them a needed nutritional substance. Biotin was conceived as an anti-egg-white-injury factor until its role in animal metabolism became more clearly understood. It is now believed to be needed for biological carbon dioxide fixation in the animal organism in decarboxylation and deamination reactions.[17] It also catalyzes the biological synthesis of oleic acid.

Biotin avitaminosis in man does not seem to occur spontaneously since the intestinal bacterial flora can synthesize adequate amounts of the vitamin. Planned experimental biotin deficiency in man has been studied.[18] Biotin is occasionally included in multiple vitamin tablets. Ordinarily, it is present in animals and plants and can be obtained as a dietary factor from fruits, vegetables, grains, yeast and liver.

The structure of biotin was elucidated by du Vigneaud.[19] A synthesis

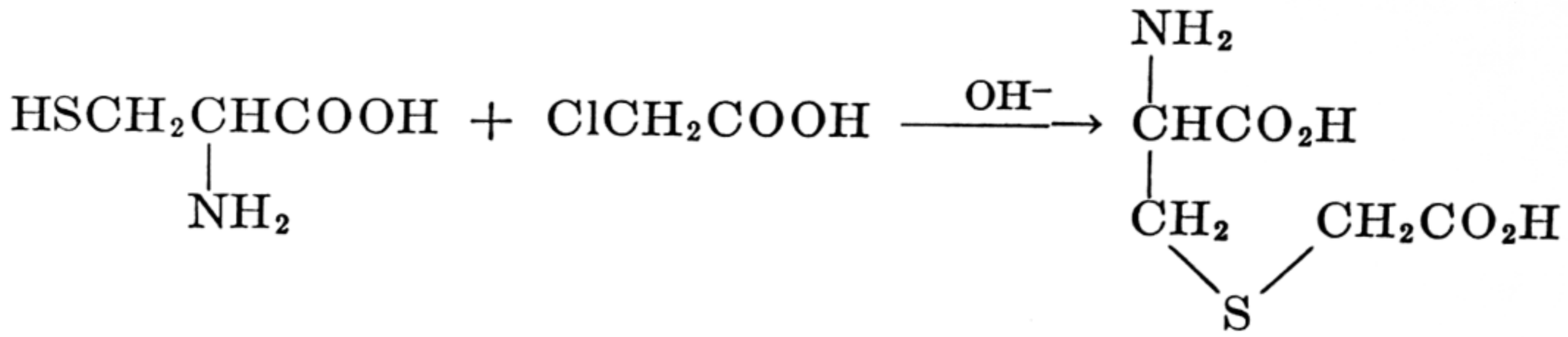
[17] Lardy, Potter, and Elvehjem, *J. Biol. Chem.*, **169,** 451 (1947). Lichstein and Umbreit, *ibid.*, **170,** 329, 423 (1947).

[18] György and Rose, *Proc. Soc. Exptl. Biol. Med.*, **43,** 73 (1940).

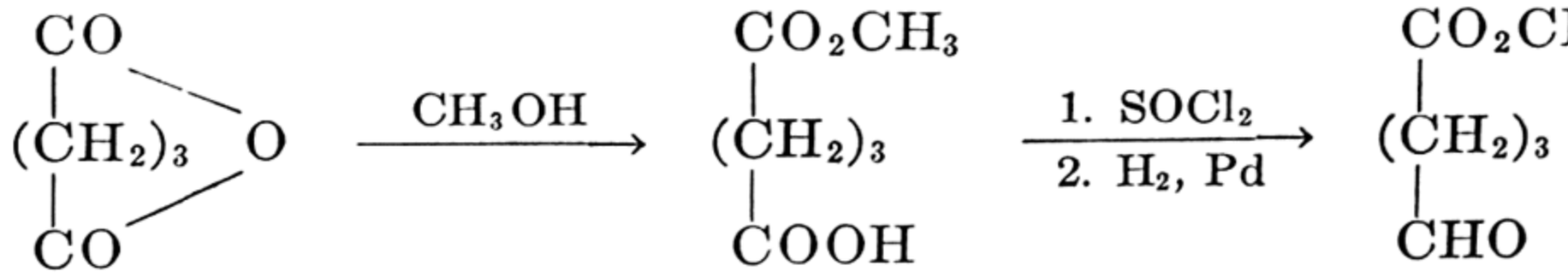
[19] du Vigneaud, Hofmann, and Melville, *J. Am. Chem. Soc.*, **64,** 188 (1942).

of the compound has been described by Folkers and his group.[20] The formula of biotin is represented by (XXVIII-43).

Two key intermediates are needed in the synthesis of biotin. One is 4-benzamido-3-ketotetrahydrothiophene (XXVIII-44), the other methyl γ-formylbutyrate. The thiophene derivative (XXVIII-44) has been obtained by the following scheme.



Methyl γ-formylbutyrate was obtained by the following steps.



[20] Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson, and Folkers, *J. Am. Chem. Soc.*, **66,** 1756 (1944); **67,** 2096, 2100 (1945). Harris, Wolf, Mozingo, and Folkers, *Science*, **97,** 447 (1943).

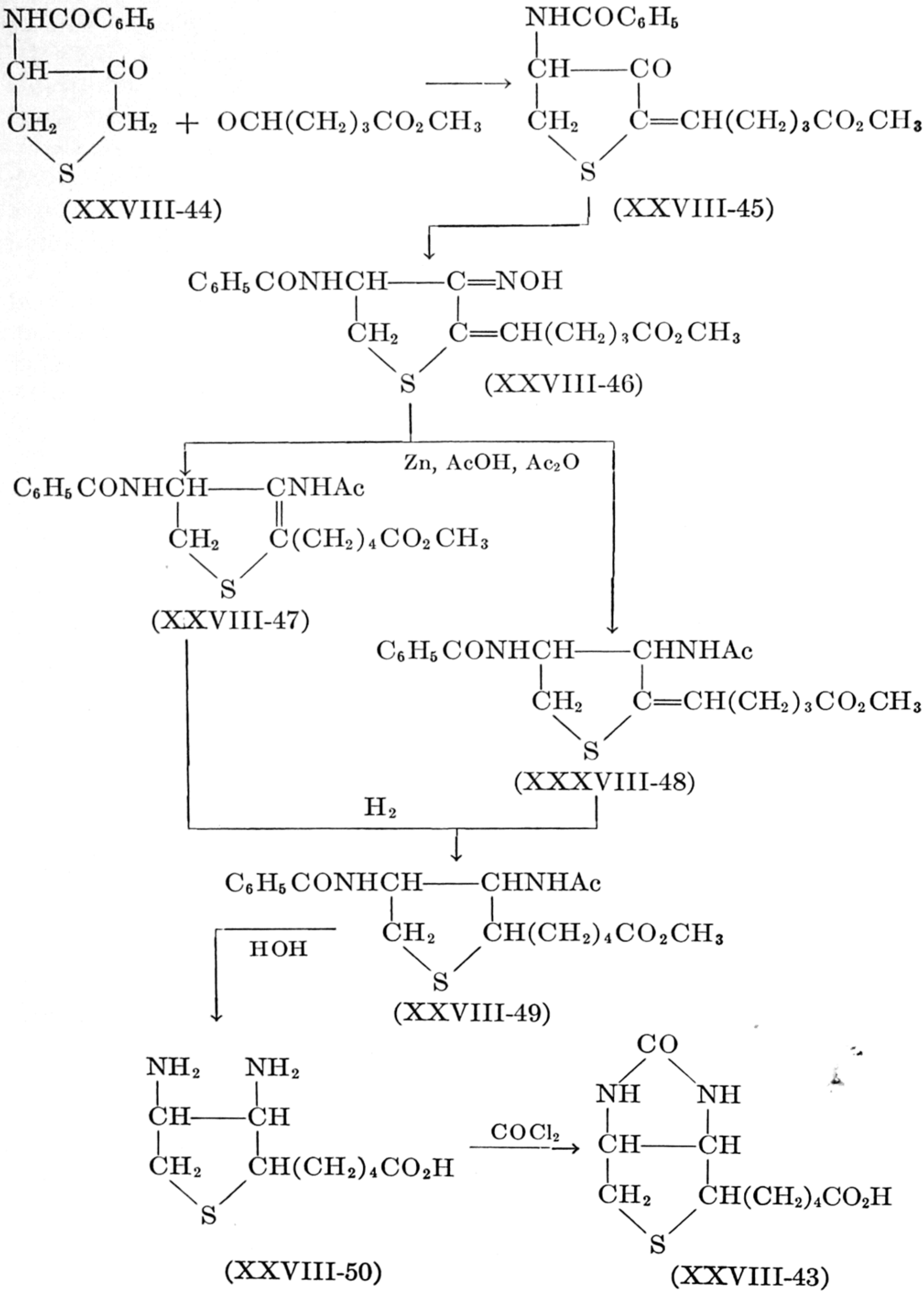


Figure 10. Synthesis of Biotin

The keto-amide (XXVIII-44) and methyl γ-formylbutyrate can be condensed in pyridine solution to yield the α,β-unsaturated ester (XXVIII-45), the oxime of which (XXVIII-46) yields two isomeric unsaturated diamides (XXVIII-47 and XXVIII-48) on reduction with zinc and acetic acid. These two isomers can be hydrogenated to the same ester of 3-acetamido-4-benzamido-tetrahydro-2-thiophenevaleric acid (XXVIII-49) which can be hydrolyzed in two steps to 3,4-diaminotetrahydro-2-thiophenevaleric acid (XXVIII-50). Treatment with phosgene closes the ureide ring of DL-biotin (XXVIII-43).

Racemic biotin exhibits about one-half the activity of the natural dextrorotatory isomer. The DL-form can be resolved well by salt formation with various bases, particularly, L(+) arginine. Diastereoisomers of DL-biotin obtained as by-products in the synthesis have proved to be physiologically inert.

h. *p*-Aminobenzoic Acid

The recognition of *p*-aminobenzoic acid (PABA), *p*-$H_2NC_6H_4COOH$,[21] as a part of the vitamin B complex followed in the wake of the observations by Woods and Fildes who found that PABA is an essential metabolite of many microorganisms, and that sulfanilamide owes its bacteriostatic activity to competition with PABA for a place in a coenzyme required for bacterial reproduction (see Chapter XXXIV).

PABA occurs widely in plant and animal cells, partly free, and partly as a section of the pteroylglutamic acid molecule (see this).

PABA-hypovitaminosis causes a graying of the fur of certain rats ("nutritional achromotrichia"). Other symptoms resemble those encountered in other B-vitamin deficiencies. No human avitaminosis has been observed.

In chronic myeloid leukemia, PABA causes a profound drop in the total leucocyte count.[21a]

The role of PABA as a chemotherapeutic agent in rickettsial infections will be discussed elsewhere in this book. PABA causes dramatic recovery in 90% of Rocky Mountain spotted fever at blood levels of 30 to 60 mg per 100 cc.[21a] More recently, PABA has been superseded in its clinical application in rickettsias by the antibiotics, Chloromycetin and Aureomycin.

i. Pteroylglutamic Acid

Pteroylglutamic acid (PGA, Folic Acid, XXVIII-51) occurs in all green leaves, in yeast, kidney and liver, either in the free state, or as a peptide conjugate containing 2 or 6 extra glutamic acid groups. Its

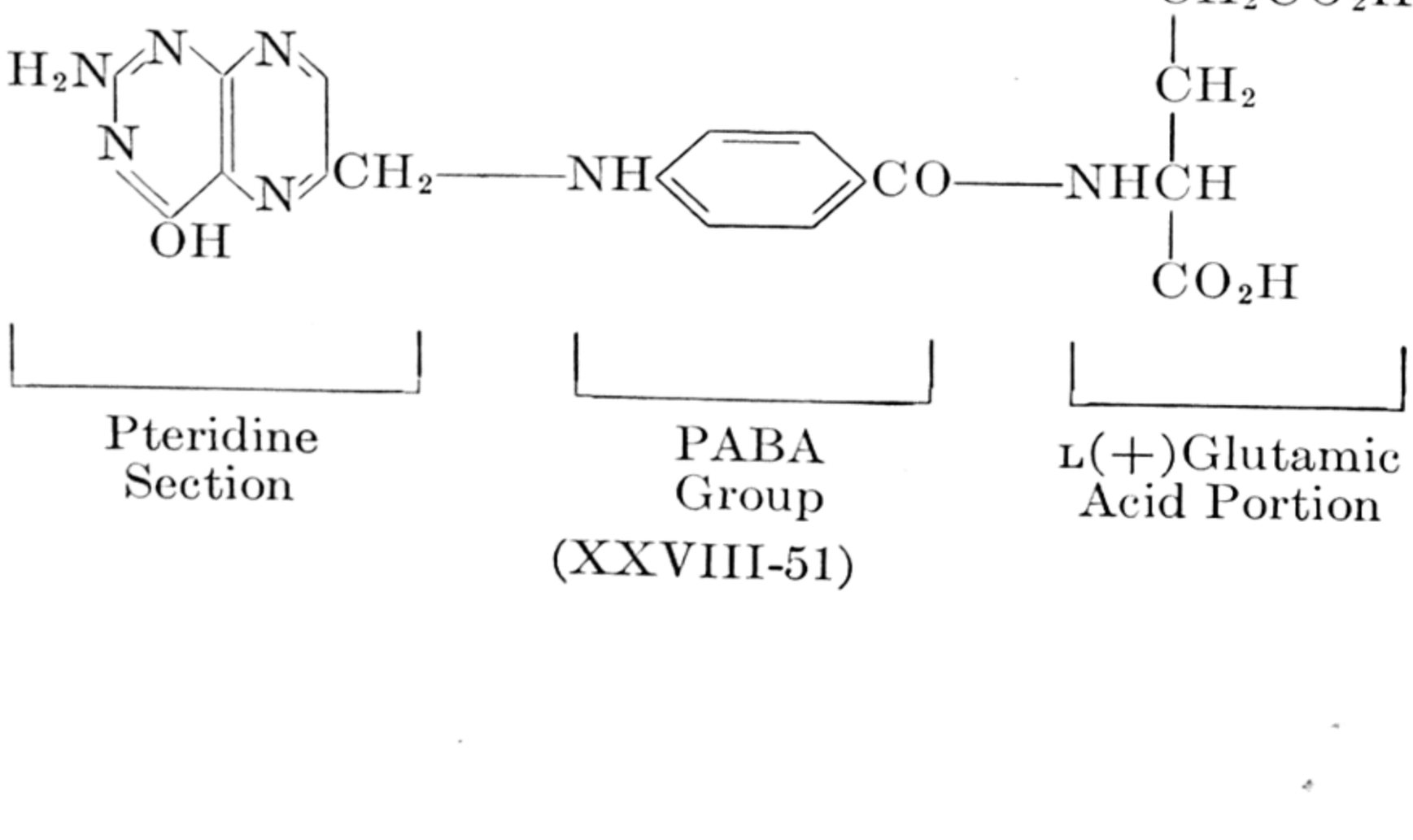
[21] Ansbacher, *Science*, **93,** 164 (1941).
[21a] Owen, *Lancet*, **2,** 607 (1948).

physiological function in animals (chicken, turkey, dog, monkey, guinea pig, fox, mink) is connected with the production of blood corpuscles; it is a hematopoietic factor. It aids in regenerating the sources of red blood corpuscle formation, especially the bone marrow, and counteracts other conditions affecting hematopoiesis. The vitamin is also effective in certain degenerative processes of blood cells but not nearly as much as vitamin B_{12}. Tropical sprue and certain nutritional anemias in man can be treated fairly successfully with folic acid.

Beyond these medicinal uses, pteroylglutamic acid appears to be a potent component of enzyme systems which are necessary for the synthesis and disposition of nucleic acids as they are needed in cell division. It is likely that PGA functions as a coenzyme for ribonuclease which regulates cell multiplication, or perhaps is a precursor of ribonucleic acid for which it may supply essential structural elements. In any case, pteroylglutamic acid is required by many types of cells including neoplasms and many bacteria. Its significance was originally recognized in a study of the growth requirements of *Lactobacillus casei*, and typical tests for the potency of PGA, its derivatives and analogs are based on the promotion of the growth of bacterial cultures by such compounds.

A number of analogs of pteroylglutamic acid have been found to exert a dual action on cell growth. Some of them support rapid cell division whereas others behave as pteroylglutamic acid antagonists and inhibit this process. The latter property has aroused interest in the possible use of these compounds as inhibitors of the spread of tumor cells. A discussion of these studies may be found in Chapter XXVII.

The molecule of PGA consists of three distinct regions, namely, pteridine, the *p*-aminobenzoyl group, and the glutamic acid group. Some organisms require pre-formed PGA, but others can synthesize their own needs of the vitamin provided the three structural components are present among the cell nutrients.



(XXVIII-51)

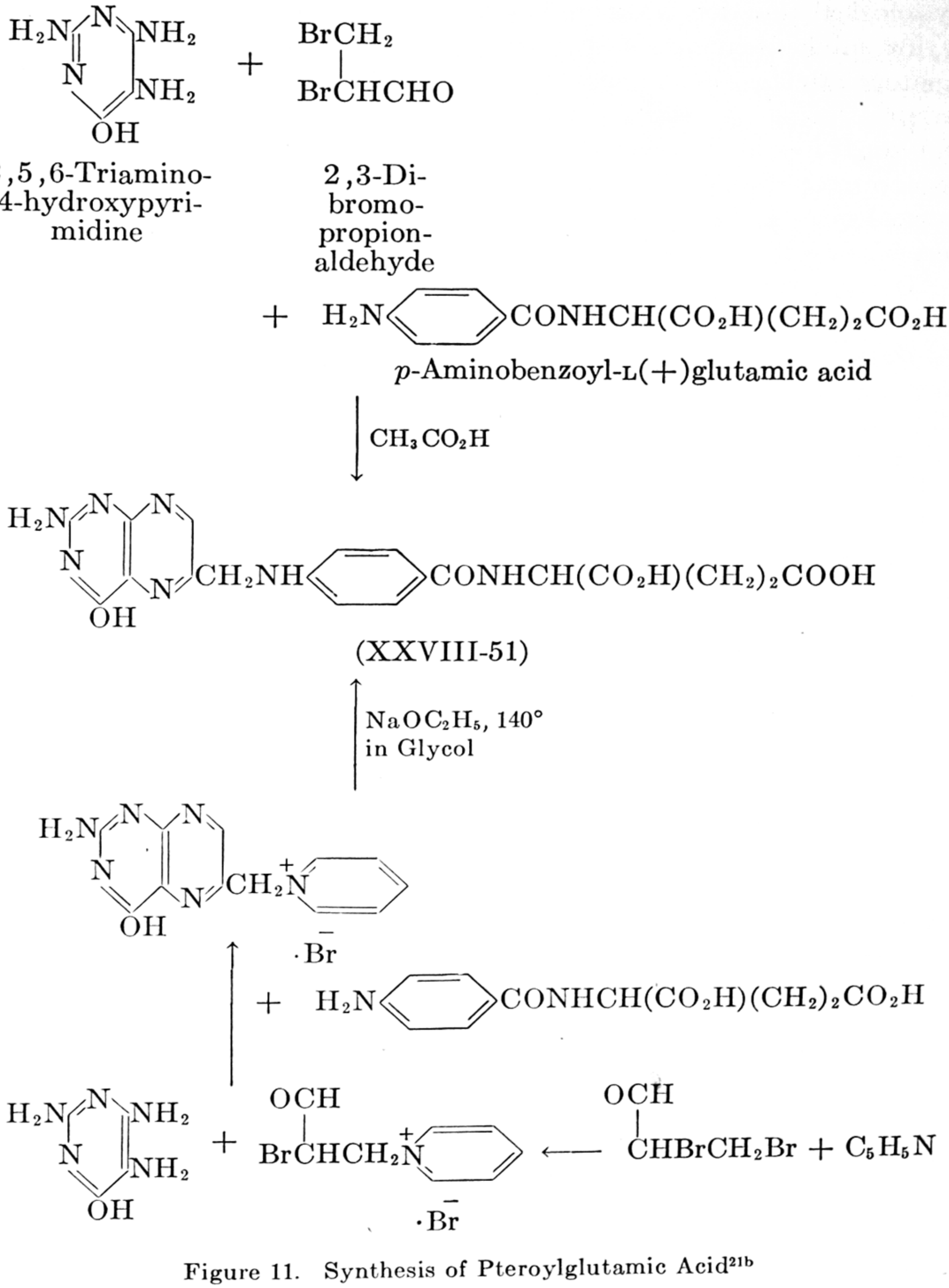


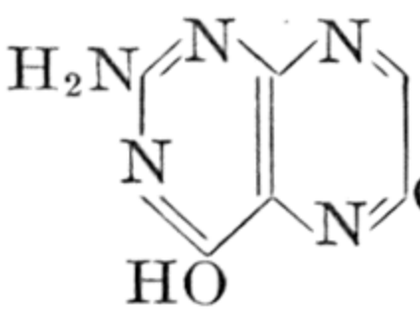
Figure 11. Synthesis of Pteroylglutamic Acid[21b]

[21b] Angier *et al.* *Science*, **103,** 667 (1946).

Factors opposing the incorporation of the structural fragments can prevent the synthesis of PGA and thereby deprive a cell of this essential metabolite. The sulfonamide drugs compete with PABA for its peptide-like place in the PGA molecule, and thus inhibit bacterial cell multiplication. By a similar mechanism, penicillin inhibits the utilization of glutamic acid in the synthesis of PGA. The theoretical implications of these biochemical interferences have had a far-reaching influence on chemotherapeutic thought.

Several syntheses of PGA have been reported in recent chemical periodicals. Two of them are schematized in Figure 11. Commercial PGA is now produced by the most favorable of these routes.

Two glutamic acid conjugates have the same activity as PGA for man and higher animals. They are pteroyltriglutamic acid (XXVIII-52), also referred to as *Lactobacillus casei* factor, and pteroylheptaglutamic acid ("vitamin B_c conjugate", XXVIII-53). Some microorganisms, however, need PGA itself for most effective utilization. The triglutamate has been isolated from aerobic bacterial fermentation processes, the heptaglutamate from yeast.



$n = 3$ (XXVIII-52)
$n = 7$ (XXVIII-53)

The specificity of analogs of pteroylglutamic acid in causing either vitamin, or anti-vitamin activity will be reviewed in Chapter XXXII.

j. Vitamin B_{12}

Vitamin B_{12} has been recognized as part of the Animal Protein Factor (APF) which appears to be related to, or is identical with the so-called extrinisic anti-pernicious anemia factor. The deep-red vitamin was isolated from liver extracts, long known to be of value in pernicious anemia, and also occurs in fish meal, eggs and whey. The feces of hens and cows contain bacteria which produce the compound. Liver extracts contain about 0.02% of the vitamin.

On the assumption that certain molds which are used commercially to produce antibiotics might also synthesize vitamin B_{12}, the mother liquors of streptomycin were subjected to biological screening tests. As pointed out in Chapter XXXVIII, streptomycin results from the fermentation of

glucose in corn steep liquor by the mold, *Streptomyces griseus*. The same fermentation process also yields commercial quantities of vitamin B_{12}.

Isolation and purification was carried out in the laboratories of Merck and Co. in the U. S. A., and by E. L. Smith and Parker in British laboratories. We owe the partial elucidation of the structure of the vitamin to Folkers and his associates.[22]

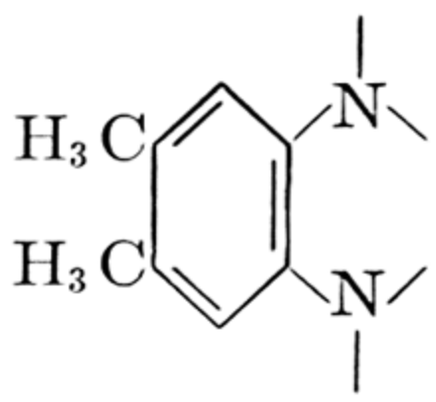
Vitamin B_{12} has the empirical formula: $C_{61-64}\,H_{86-92}\,Co\,N_{14}\,O_{13}\,P$. The difference between vitamin B_{12} and another factor of this group, vitamin B_{12c}, is probably the point of esterification of the ribofuranosyl chain shown in (XXVIII-54) with phosphoric acid. Among the products of the acid hydrolysis, l-ribofuranosyl-5, 6-dimethylbenzimidazole has been found in the form of a phosphate ester. Since this ester does not contain a 1,2-glycol group, the phosphate portion must be attached to C_2 or C_3 of the side chain.[22a]



(XXVIII-54)

Catalytic hydrogenation of Vitamin B_{12} has furnished another red compound, vitamin B_{12a} which has a biological activity similar to that of its parent compound.

It may be significant that both vitamin B_{12}, riboflavin, and L-lyxoflavin from heart muscle contain the 4,5-dimethyl-*o*-phenylenediamine structure (XXVIII-54a).



(XXVIII-54a)

Mild hypovitaminosis B_{12} produces lassitude, and in school children poor scholastic performance. More severe deficiencies lead to the classical syndrome of pernicious anemia. The bone marrow of anemia victims contains a congestion of megaloblasts, the intermediate bodies from which red blood cells are formed. This congestion is relieved by doses of 0.1 mg. of vitamin B_{12}; pteroylglutamic acid produces the same effect in other anemias

[22] Brink and Folkers, *J. Am. Chem. Soc.*, **71,** 2951 (1949). Folkers, *Ind. Eng. News*, **28,** 1634 (1950). Folkers *et al.*, *ibid.*, **73,** 335 (1951).

[22a] Brink, Holly, Shunk, Peel, Cahill, and Folkers, *J. Am. Chem. Soc.*, **72,** 1866 (1950). Buchanan Johnson Mills and Todd *J.Chem. Soc.*, 2845 (1950).

only at dosages of from 20 to 50 mg. Administration of vitamin B_{12} also causes resumption of the production of leucocytes and platelets, and relieves the degenerative processes of the spinal cord associated with pernicious anemia. The vitamin is also superior to PGA in its effect on nutritional macrocytic anemia and sprue because it is utilized directly by marrow cells. Animals need vitamin B_{12} for normal growth, in their production of hatchable eggs, etc. The existence of a vitamin-like substance in the "animal protein factor" had long been suspected. Recently, 5,6-dimethylbenzimidazole has been found to possess about one thousandth the APF activity of vitamin B_{12}.

Relations of vitamin B_{12} to other vitamins and hormones are becoming known only slowly. One significant incompatibility has been noted. Ascorbic acid rapidly decomposes vitamin B_{12} at room temperature.[23] On the other hand, vitamin B_{12} reduces damage from choline-deficient diets in the rat.

k. Iron in Anemia

Hemoglobin, cytochrome, catalase and other porphyrine-protein complexes containing iron cannot be synthesized by the body tissues unless iron is available from an outside source. Blood cells and other structures containing iron are constantly destroyed in the normal processes of cell metabolism, the liberated inorganic iron is excreted in part and has to be replaced. Anemias resulting from a lack of available iron are called hypochromic anemias.

Apart from food as a normal source of iron, many iron salts and preparations are on the market which are given therapeutically in hypochromic anemia. Ferrous sulfate is the least expensive and most readily utilized form of oral iron therapy but the carbonate, citrate, soluble double salts etc. are also used. Even metallic iron powder ("reduced iron"), given in capsules is of value in anemic states. Occasionally, iron compounds are given parenterally if the oral route does not prove satisfactory.

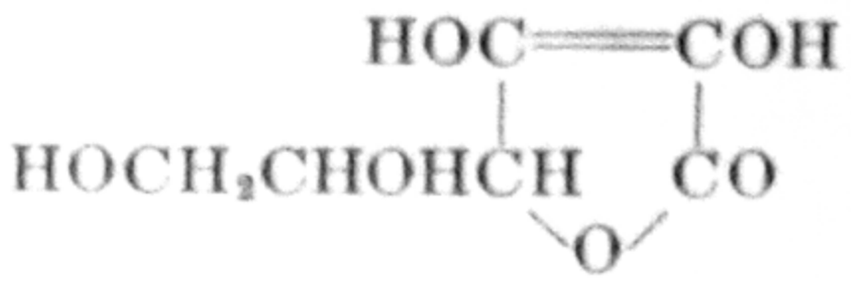
3. Ascorbic Acid—Vitamin C

a. Functional Reactions

Ascorbic acid (XXVIII-55) is a water-soluble lactone containing an acidic enediol group and is, like other compounds of this type, easily and reversibly oxidizable. This property had hampered progress in its isolation and the elucidation of its structure before measures to stabilize the vitamin became known.

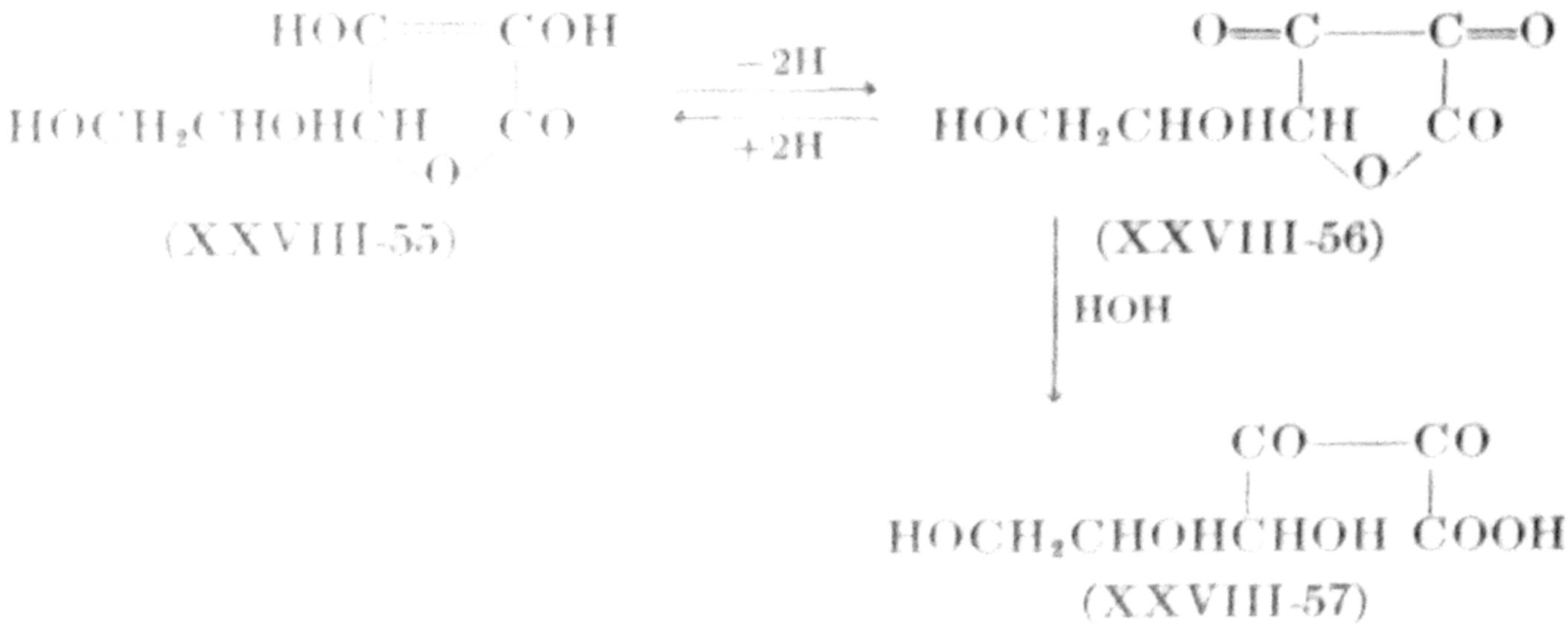
Ascorbic acid is necessary for the normal growth of many higher plants and microorganisms but its great significance lies in its action on the human

[23] Gakenheimer and Feller, *J. Am. Pharm. Assoc.*, **38,** 660 (1949).



(XXVIII-55)

organism and that of certain animals. The vitamin takes part in respiratory processes involving several enzyme systems including peroxidase, various hexose dehydrogenases, glutathione, catalase, urease, phosphatase, cytochrome oxidase and others. In all these reactions ascorbic acid (XXVIII-55) gives up two atoms of hydrogen and is converted to the diketo lactone, dehydroascorbic acid (XXVIII-56). Since this dehydrogenation is reversible, the latter has the same biological activity as the enediol. When, however, the lactone ring of dehydroascorbic acid is hydrolyzed, diketogulonic acid (XXVIII-57) is formed and vitamin activity is lost irreversibly.



(XXVIII-55) (XXVIII-56) (XXVIII-57)

The role of ascorbic acid as a hydrogen carrier in coenzyme systems extends to carbohydrate and amino acid metabolism. In addition, the vitamin probably acts as an antioxidant for active groups of enzymes in which it does not participate directly as a carrier. It also appears to be a factor in the formation of colloidal substances which cement body cells together such as cartilage, dentine and collagen; these phenomena are associated with disturbances of the calcium metabolism which occur in deficiencies of ascorbic acid, and which affect the health of teeth and bones, and foster hemorrhages so characteristic of avitaminosis C. In addition, ascorbic acid can render harmless toxic doses of a variety of materials, for example, lead and arsenic compounds, toxins, hydrocarbons etc. The mechanism of this action is unknown, but it is suspected that at least some of these substances are excreted as ascorbic acid conjugates.

In acute, severe deficiency of ascorbic acid, a pathological syndrome called scurvy is observed. It consists mainly of an increased permeability of the blood vessels and results in bleeding and the failure of wounds to heal.

The first hemorrhagic symptoms usually occur in the mouth, and are followed by loosening of the teeth. Guinea pigs afflicted with experimental scurvy try characteristically to raise themselves in order to relieve pressure on aching joints. Scurvy and other accompanying deficiency symptoms can be avoided if a diet containing adequate amounts of ascorbic acid (3 to about 10 mg./kg./day) is ingested. Citrus juice, leaves, green vegetables, paprika, apples etc. are among the best dietary sources of the vitamin.

It is interesting that only man, the other primates, the guinea pig and a few microbes require an external supply of ascorbic acid. For all other animals and plants, ascorbic acid is a hormone, that is, they are able to synthesize this essential biocatalyst.

Vitamin C is prescribed therapeutically in cases of clinical or subclinical scurvy, in various disturbances and ulcerations of the gastrointestinal tract if the vitamin is poorly absorbed, in rheumatic fever, metallic poisonings, as an adjunct in the treatment of allergies and other conditions. It is widely used to improve general health and resistance to infections, and can be taken in comparatively huge doses since its toxicity is extremely low.

Figure 12. Ascorbic Acid from Glucose

b. Synthesis

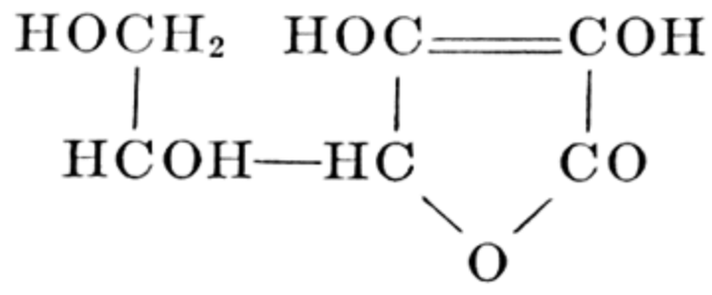
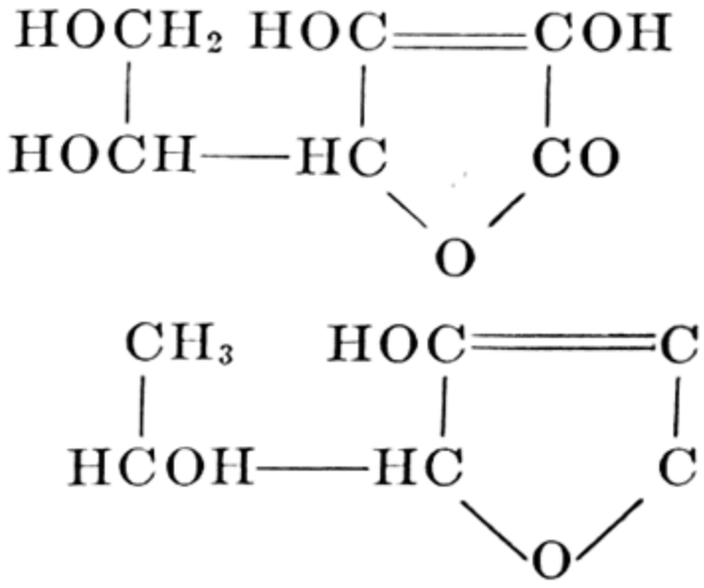
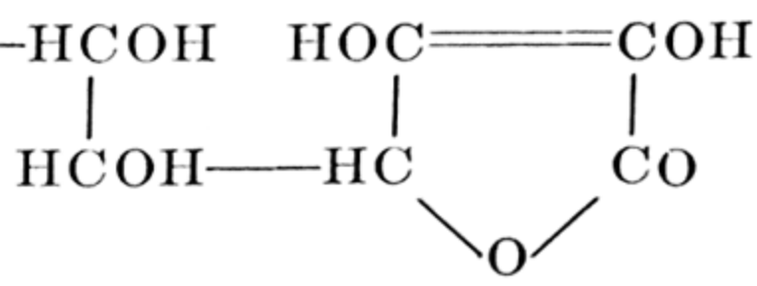
The ascorbic acid used in therapy is now manufactured almost entirely synthetically. Of the several laboratory and commercial syntheses, the one from glucose has found widest acceptance. Glucose (XXVIII-58) is hydrogenated catalytically to D-sorbitol (XXVIII-59), and the latter is oxidized by acetic acid bacteria to L-sorbose (XXVIII-60). This ketose is then oxidized either with nitric acid, or catalytically, to 2-ketogulonic acid (XXVIII-61) which lactonizes in acid solution to vitamin C (XXVIII-55).

c. Analogs

The antiscorbutic action of ascorbic acid is not matched by any structurally related compound unless dehydroascorbic acid is considered which can be reduced to the vitamin. Likewise, the methyl ester of 2-ketogulonic acid (see above) is highly active presumably because it is particularly readily lactonized.

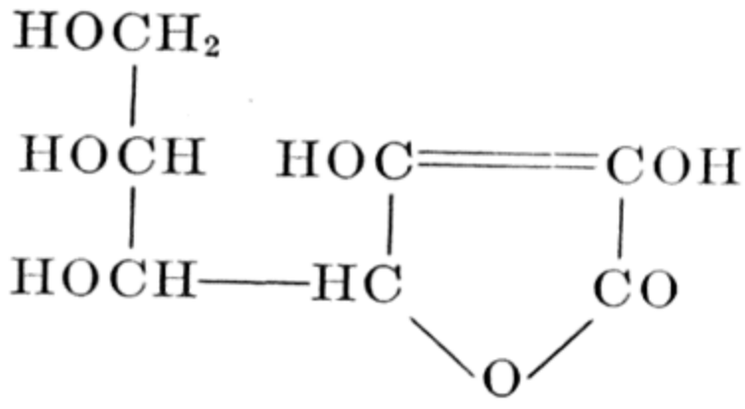
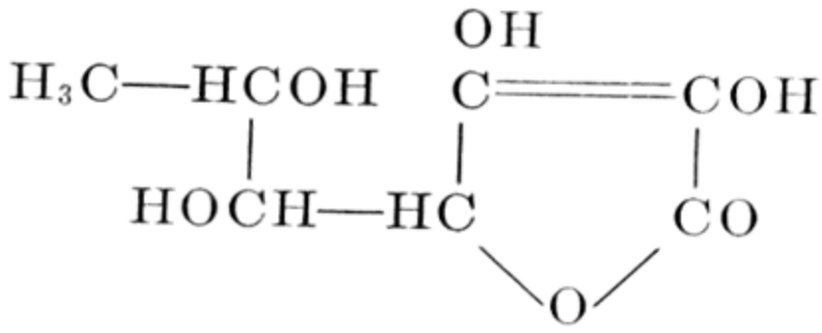
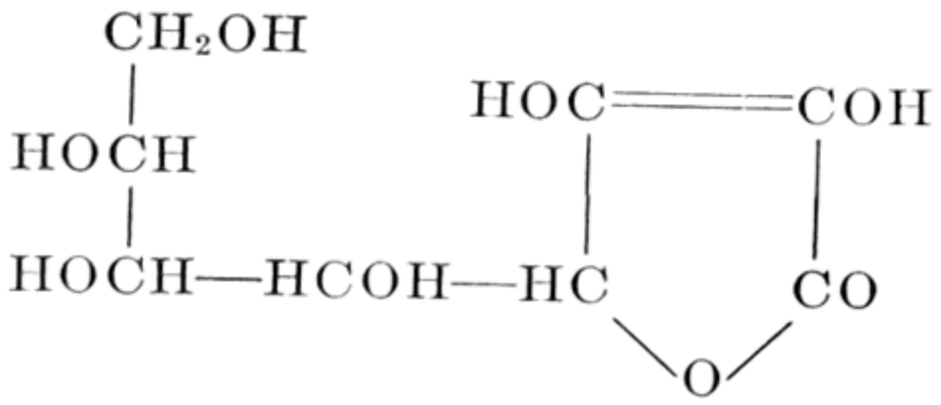
Several stereoisomers and homologs of ascorbic acid have been tested for antiscorbutic activity. Their structures and activities are tabulated below. One can conclude that carbon atom 4 which carries the diol side chain must have the same (D) configuration as ascorbic acid if activity is to be observed. There must be a side chain of at least two carbon atoms attached to C-4, and C-5 must contain a hydroxyl group. All hydroxyls must be free.

TABLE I. Antiscorbutic Activity of Isomers and Analogs of Ascorbic Acid

Name	Configuration	Activity
L-Ascorbic Acid		1
Isoascorbic Acid		0.05
6-Desoxy-L-ascorbic Acid		0.3
L-Rhamnoascorbic Acid		0.2

(Table Continued)

TABLE I (*Continued*)

L-Glucoascorbic Acid		0.025
L-Fucoascorbic Acid		0.02
D-Glucoheptoascorbic Acid		0.01

4. Vitamin P

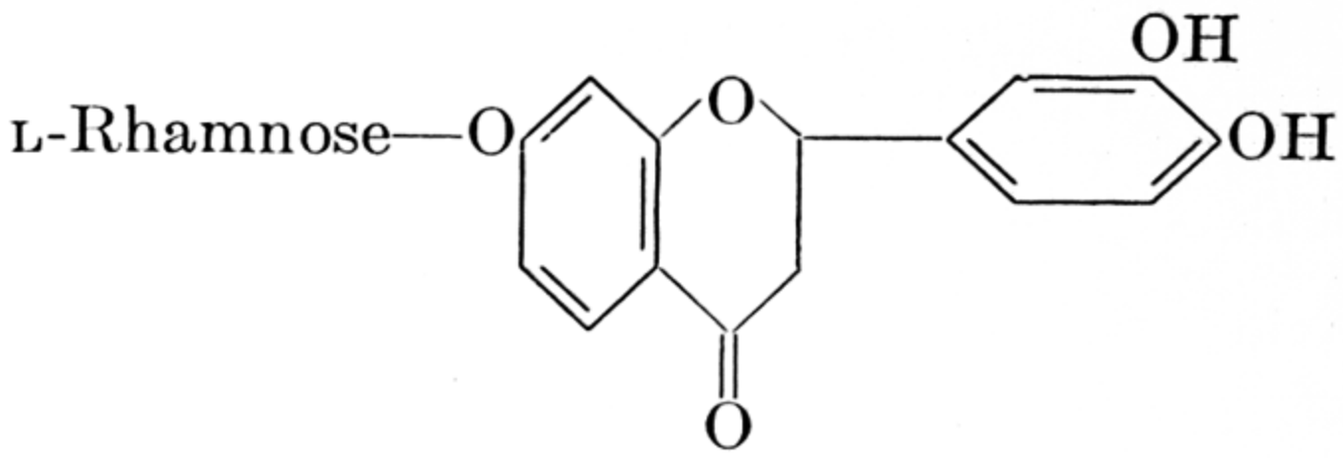
In addition to true scurvy, similar hemorrhagic conditions of the skin have been observed which cannot be cured by ascorbic acid. Capillary permeability is increased, and the bleedings are accompanied by pain in the shoulders and legs, and by low serum calcium. These symptoms can be prevented or cured by administration of a number of flavanone glycosides which are sometimes spoken of as the permeability vitamins, or vitamin P factors.

Vitamin P can be obtained in form of a crude extract from citrus fruits, particularly their skin, or from paprika.[24] The active principle is called citrin and constitutes a mixture from which two flavanone glycosides have been isolated, namely, hesperidin (XXVIII-63) and eriodictin (XXVIII-64). Another glycoside of similar activity is Rutin (XXVIII-65) which occurs in many flowers, shrubs and in cured tobacco.[25]

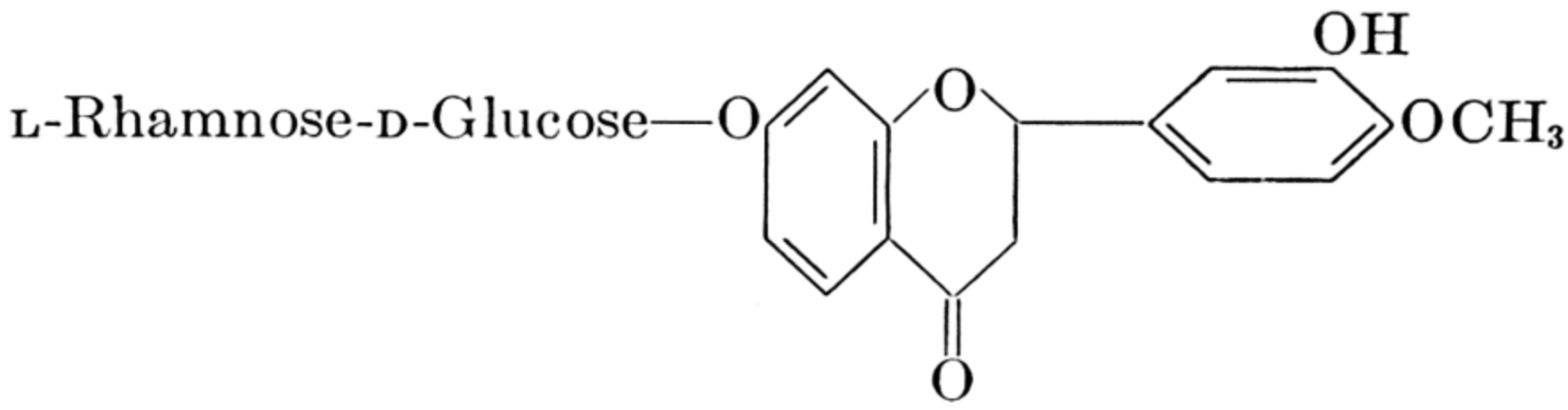
Eriodictin is hydrolyzed to the aglycone, eriodictyol, and to rhamnose. Hesperidin (XXVIII-63) yields the 4′-methyl ether of eriodictyol, called hesperitin, plus glucose and rhamnose. Rutin (XXVIII-65) also furnishes these saccharides in addition to an aglycone which contains one more hydroxyl group than eriodictyol.

Hesperidin has been reported to provide relief in allergic and vaso-

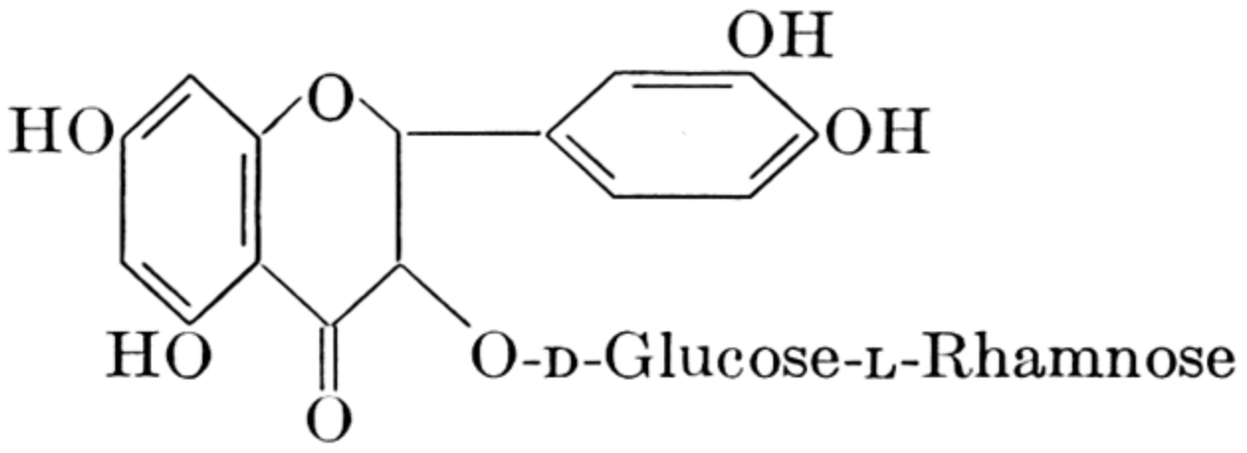
[24] Bentsáth, Rusznyák, and Szent-Györgyi, *Nature*, **138,** 798 (1936).
[25] Griffith, Couch, and Lindauer, *Proc. Soc. Exptl. Biol. Med.*, **55,** 228 (1944).



(XXVIII-64)



(XXVIII-63)

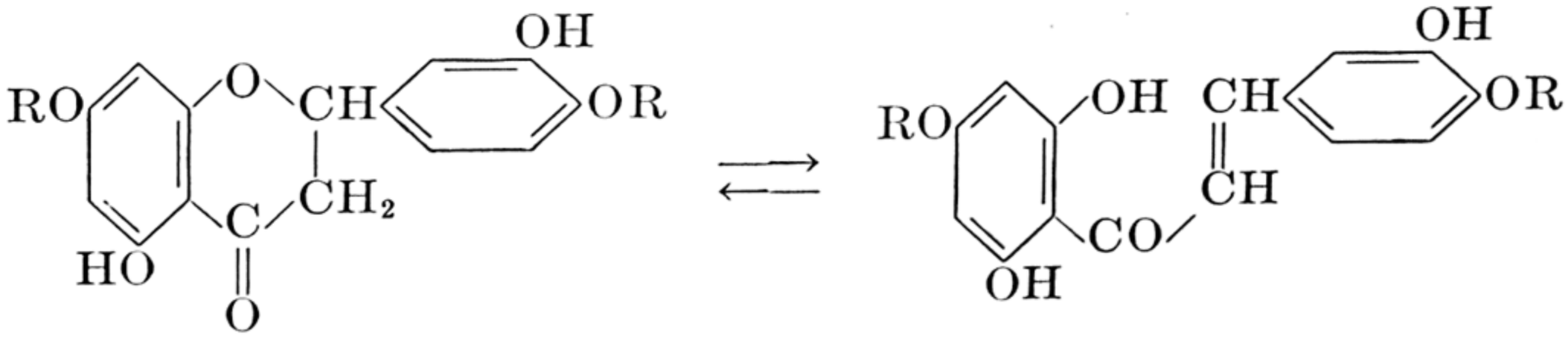


(XXVIII-65)

motor rhinitis. Other clinical applications have been reviewed recently.[25a]

Rutin has been recommended for the treatment of high blood pressure in arteriosclerosis, angina pectoris and congestive heart failure but its value in these conditions has remained doubtful.

The mechanism of the physiological action of these flavanones has been explained by assuming that they isomerize in the tissues to open chain chalcones (XXVIII-66) which could lend themselves to quinonoid oxidation. The glycosides combine in the tissues with proteins and act in this combination as hydrogen carriers.



(XXVIII-66)

5. Vitamins D

a. From 7-Dehydrocholesterol and Ergosterol

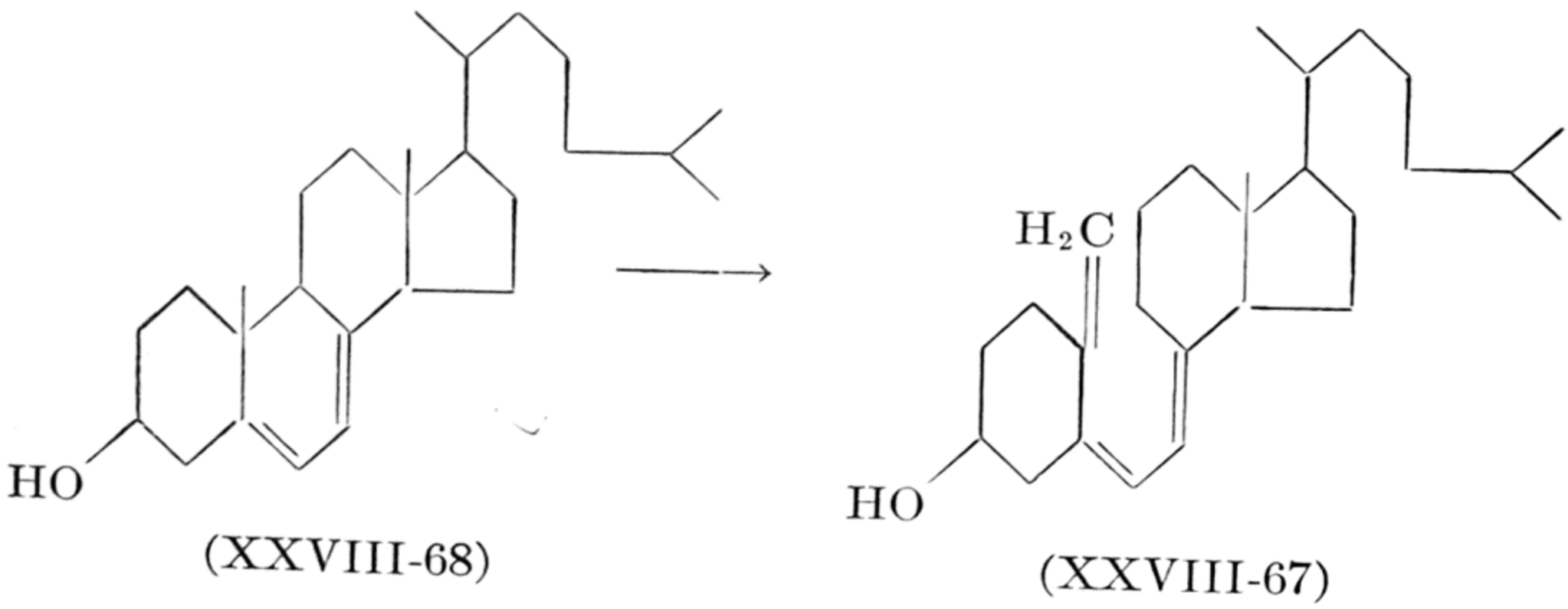
Several compounds which are structurally related to the sterols have the ability to cure or prevent rickets. These factors are known as vitamin D as a therapeutic unit.

[25a] Saylor, *Arch. Otolar.*, **50,** 813 (1949). Levitan, *New Eng. J. Med.*, **241,** 780 (1949).

Rickets is caused by insufficient ossification due to inadequate deposition of calcium phosphate at the growing ends of the bones. It is more often observed in babies or young children who experience skeletal deformities with excessive formation of cartilage and enlargements of the junctions between the bones. *D*-Hypovitaminosis also contributes to dental caries, and infantile tetany has been attributed to this deficiency. Rickets in adults is more uncommon; it is called osteomalacia and consists of a loss of calcium phosphate from the bones which thus become brittle.

Vitamin D is administered routinely during pregnancy, and to infants and children. The sources of virtually all the medicinally used vitamin D are fish liver oils; since they are also rich in vitamin A, they constitute a convenient mode of providing both types of fat-soluble vitamins. Liver oil of tuna, cod, percomorph, shark, etc. are saponified and the A and D vitamins remain in the unsaponifiable non-glyceride fraction. Vitamin D can be concentrated by formation of insoluble esters[26] (e.g., the phthalate), or by molecular distillation of the fish liver oils.[27]

The true natural antirachitic factor from tuna oil was isolated by Brockmann[28] and was called vitamin D_3 (XXVIII-67). It is a triene derived from 7-dehydrocholesterol (XXVIII-68) and is obtained from the latter by radiant energy, best at the wave length of its maximum absorption.



(XXVIII-68) (XXVIII-67)

Although a fractionation analysis of cod liver oil by molecular distillation has indicated that perhaps six different vitamins D are present in this material, only one other pure vitamin has been identified in fish oils. It is vitamin D_2 (XXVIII-69, viosterol, Calciferol) which is derived from ergosterol (XXVIII-70) by irradiation. In this carefully studied process, several intermediates have been identified which are pictured in Figure 13 on page 551.

[26] Ender, *Z. Vitaminforsch.*, **2,** 241 (1933).
[27] Hickman and Gray, *Ind. Eng. Chem.*, **30,** 796 (1938). Hickman, *ibid.*, **32,** 1451 (1940).
[28] Brockmann, *Z. physiol. Chem.*, **241,** 104 (1936).

Although the formulas of vitamins D_2 and D_3 are so written as to indicate their relation to their steroid (perhydrocyclopentanophenanthrene) precursors, the actual shape of the molecule of viosterol is extended as shown by X-ray analysis.[29]

No total synthesis for either ergosterol (provitamin D_2) or for 7-dehydrocholesterol (provitamin D_3) has been worked out, but the latter can be prepared from cholesteryl acetate (XXVIII-71) by three routes two of which are pictured in Figure 14. The best yields of this intermediate are obtained by route A (page 552).

The finding that vitamin D_2 and D_3 are formed by irradiation of steroid derivatives put on a clearer basis the older observations that rickets is prevented or benefited by sunlight. Both in man and in many animals, the provitamins are concentrated largely in the skin, where they can be reached best by light. They all have a hydroxyl group in the 3-position (ring A), and a pair of conjugated double bonds in positions 5,6 and 7,8 of nucleus B of their sterol molecule. Irradiation with ultraviolet light opens ring B and produces a vinyl group at position 10. As shown in Figure 13, several intermediates lie in the path of the formation of the vitamins from the provitamins, but none of these intermediates have vitamin D activity. The vitamins (D_2 or D_3) themselves are unstable to overradiation and are converted to steroid products (suprasterol, pyrocalciferol etc.) of divergent configurations. The skin appears to possess a protective mechanism by which these secondary reactions are avoided *in vivo*.

The best industrial method of radiant activation of ergosterol and 7-dehydrocholesterol utilizes a mercury vapor lamp around which lies a quartz irradiation chamber. The provitamin D dissolved in oils or various solvents, best in ether, passes through the chamber in a continuous flow. The optimum wave lengths are equal to the maximum absorption of the provitamins, that is, 281 mμ for ergosterol and 286.7 mμ for 7-dehydrocholesterol. A wave length range between 275 and 300 mμ gives the best commercial yields of vitamin D. The energy required to produce one gram of viosterol from ergosterol has been calculated as 3×10^{21} quanta.

Instead of irradiating pure provitamins D_2 or D_3 or their concentrates, foods containing these substances can be irradiated successfully to step up their vitamin D content. Milk, both fresh and dried, is irradiated on a vast scale, and "fortified" flour, yeast and cereals are also marketed. Even cows can be irradiated, and the vitamin D content of their milk reflects this activation; the animals can also be fed irradiated yeast with similar results: their milk now contains "metabolized vitamin D".

[29] cf. Fieser and Fieser, *Natural Products Related to Phenanthrene.* Reinhold, New York, 1949, pp. 167–183.

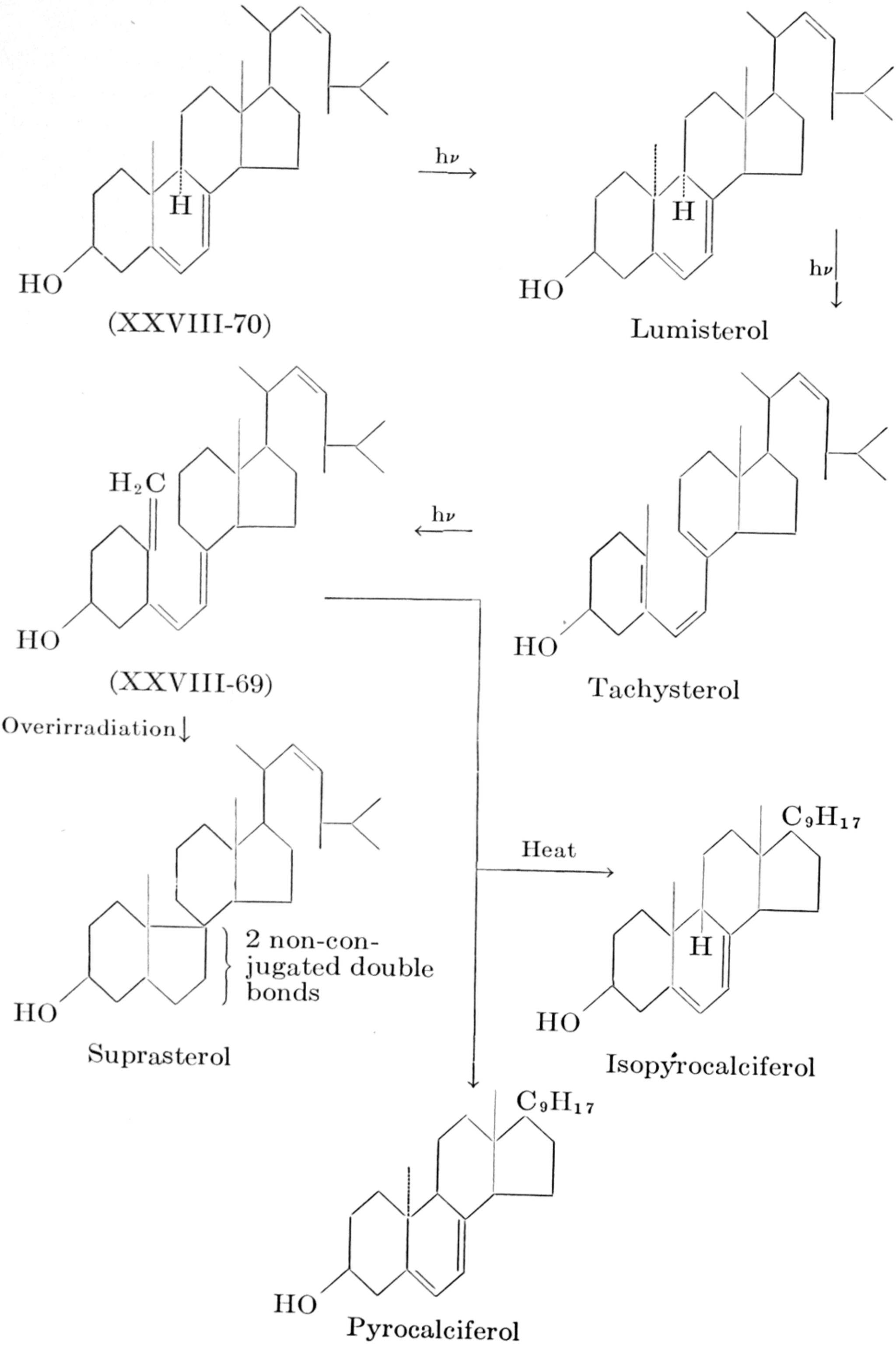
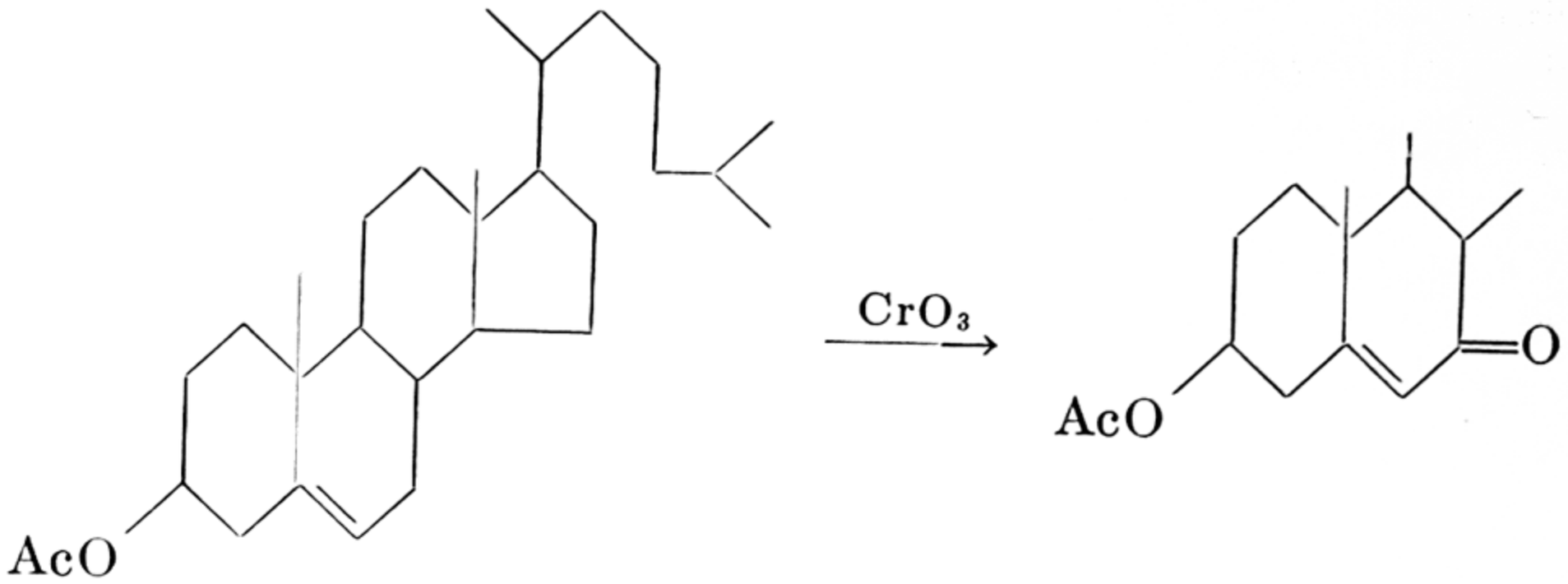
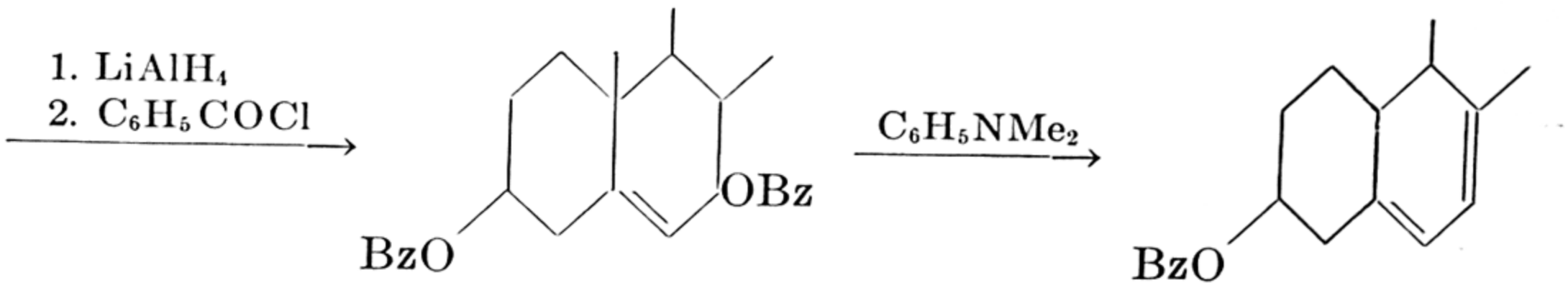


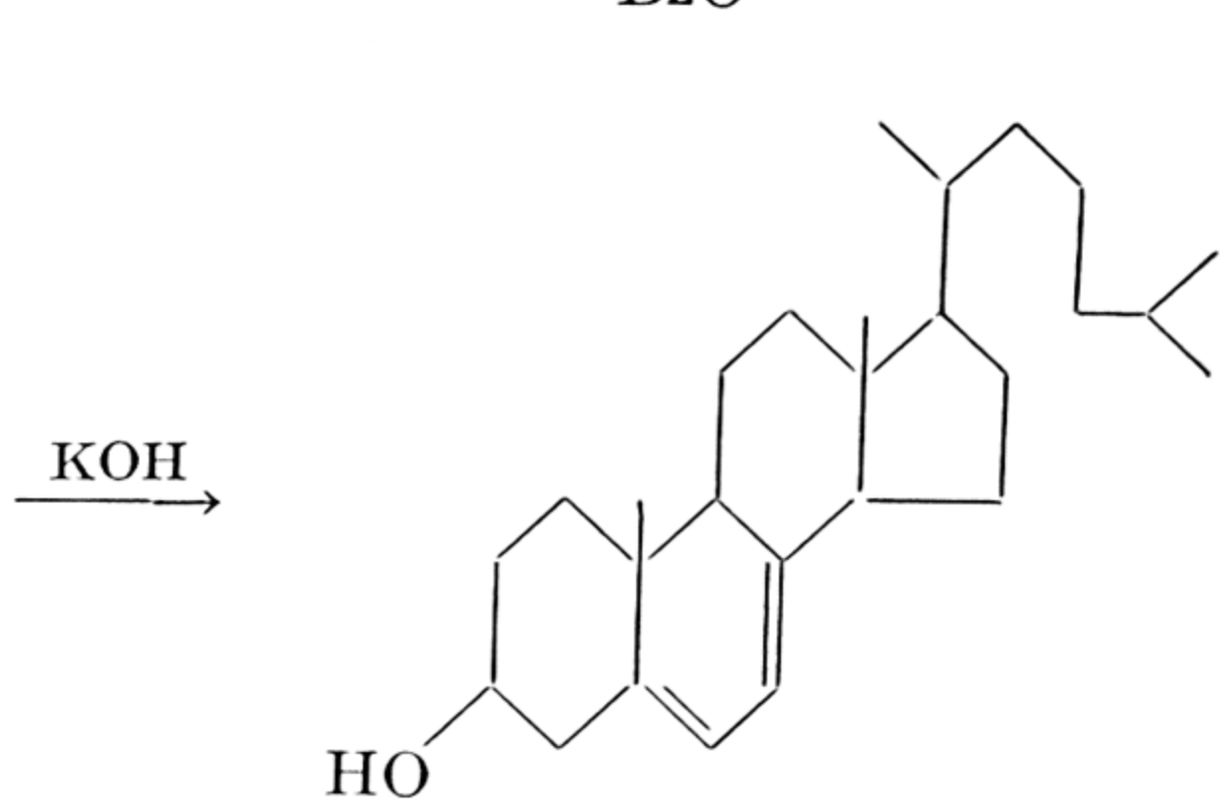
Figure 13. Irradiation of Ergosterol

Route A[30,31]



(XXVIII-71)





(XXVIII-68)

Route B[32]

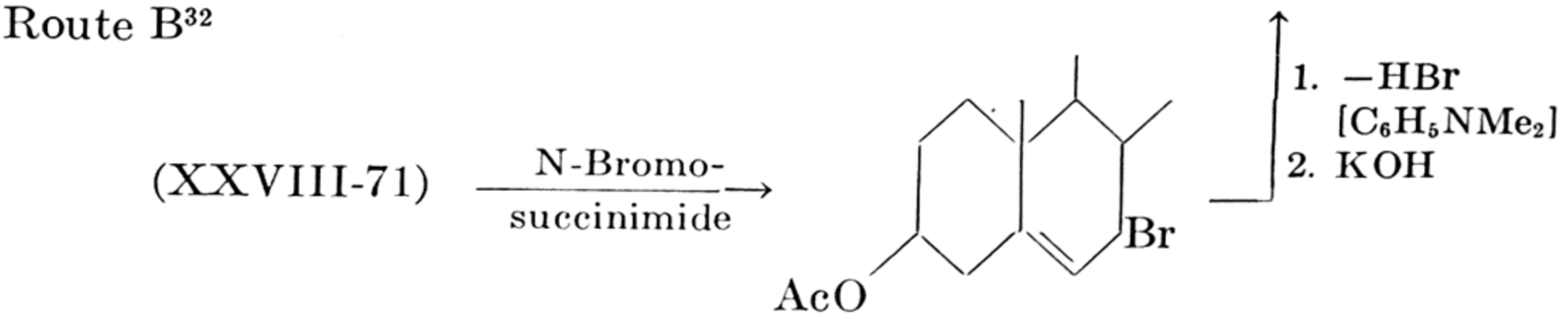


Figure 14. Partial Synthesis of 7-Dehydrocholesterol from Cholesterol

[30] Windaus, Lettré, and Schenck, *Ann.*, **520,** 98 (1935). Buser, *Helv. Chim. Acta*, **30,** 1385 (1947).

[31] Fieser, Fieser, and Chakravarti, *J. Am. Chem. Soc.*, **71,** 2226 (1949).

[32] Henbest, Jones, Bide, Peevers, and Wilkinson, *Nature*, **158,** 169 (1946). Buisman, Stevens, and Vliet, *Rec. trav. chim.*, **66,** 83 (1947). Redel and Gauthier, *Bull. soc. chim.*, **15,** 607 (1948).

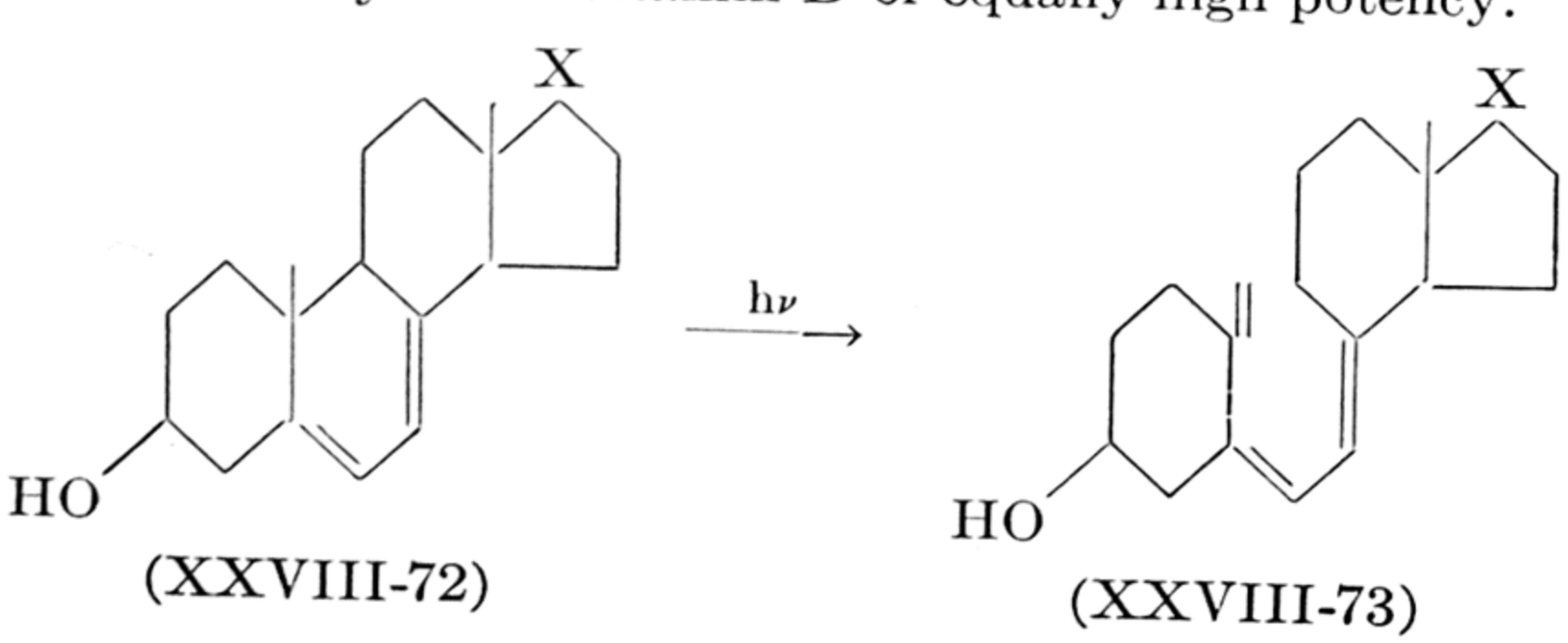
The ergosterol content of foods is responsible for the formation of viosterol in food stuffs by irradiation. Ergosterol is also manufactured as a provitamin D by extraction of yeast or the mycelium of the mold, *Aspergillus niger*. When obtained from the latter source, it often contains up to 5% of α-dihydroergosterol.

For clinical use, oil solutions of vitamin D, or solutions in propylene glycol and several other solvents are being manufactured. The vitamin has also been dispersed colloidally in water and is incorporated in emulsions, tablets and vitamin capsules. Since it is sensitive to oxidation in the presence of other irradiation products, it must be stabilized by antioxidants.

Poultry cannot utilize provitamins D from their food but have to be provided with the vitamin itself, usually in the form of fish liver oils.

b. Other Provitamins and Vitamins D

Vitamin D_3 is considerably more potent than viosterol (D_2), and many experiments have been performed to explore relations of chemical structure and antirachitic activity. If one irradiates various sterols which conform structurally to the definition of a provitamin D (XXVIII-72), the corresponding vitamin should have the formula (XXVIII-73), where X represents the side chain in position 17 characteristic of the respective sterol. The irradiation product of 22-dihydroergosterol
($X = -CH(CH_3)(CH_2)_2CH(CH_3)CH(CH_3)_2$) has become known as vitamin D_4. It is almost as potent as vitamin D_3 and much more so than viosterol. Irradiated 7-dehydrositosterol
($X = -CH(CH_3)(CH_2)_2CH(C_2H_5)CH(CH_3)_2$) is also highly active but its 22-dehydro derivative, 7-dehydrostigmasterol
($X = -CH(CH_3)CH{=}CHCH(C_2H_5)CH(CH_3)_2$) barely exhibits activity. A stereoisomer of 7-dehydrocholesterol, namely, 7-dihydroepicholesterol
($X = -CH(CH_3)(CH_2)_3CH(CH_3)_2$) possesses only about 5% the activity of vitamin D_3. As far as it is known now, the natural vitamin D_3 holds the undisputed position of the most active antirachitic vitamin. However, the irradiation of a provitamin D of unknown constitution which has been isolated from mussels yields a vitamin D of equally high potency.



(XXVIII-72) (XXVIII-73)

In evaluating compounds for antirachitic activity, two different standards had to be set up because chicks, turkeys and other poultry do not respond to provitamin D as well as do mammals, and even the responses to vitamin D_2 and vitamin D_3 are not consistent. The U. S. P. Unit ot vitamin D measures plant-type vitamin D and is defined as 0.025 γ of pure viosterol. The A. O. A. C.[33] chick unit is the standard of animal type vitamin D as it is found in cod liver oil. One gram of vitamin D_3 corresponds to 45×10^6 U. S. P. units, and 58×10^6 A. O. A. C. chick units, respectively.

There exists a relation between the effects of vitamin D and that of other vitamins and of certain hormones. In contrast to other vitamins, vitamin D is toxic in larger doses, and this toxicity syndrome is relieved by members of the vitamin B complex. Most apparent is the symptomatic similarity of the actions of vitamin D and the parathyroid hormone. However, these two factors operate by different mechanisms, the parathyroid hormone influencing serum calcium, whereas vitamin D acts primarily on serum phosphate levels. Since both biocatalysts thus produce changes of the calcium phosphate content of blood, tissues and bones, their effects are interdependent.

6. Tocopherol—Vitamin E

The four known tocopherols are classified under the collective name of vitamin E. Their significance in human metabolic processes has not been definitely established, and almost all the biological work has been conducted in the rat. Vitamin E deficiency in this animal leads to sterility; this is caused in the male rat by loss of spermatozoal motility, degeneration of the spermatozoa, and pathological changes of the epithelium of the seminiferous tubes. It leads ultimately to a loss of sex instinct. Administration of tocopherol cannot reverse these changes.

In the female animal, the time of development of the embryo is prolonged and the young may be born dead if *E*-hypovitaminosis is mild. More severe deficiency leads to degeneration and resorption of the fetus but administration of the vitamin can still restore normal estrus and ability to conceive. Further avitaminosis produces irreversible pathological changes in the uterus, and permanent sterility.

The most typical symptom of *E*-hypovitaminosis in animals is muscular dystrophy and creatinuria, and it appears possible that similar conditions in man are caused by *E*-deficiencies, since tocopherol can be used successfully in the treatment of muscular dystrophy. Certain cases of abortion and other interruptions of pregnancy also respond favorably to tocopherol.

[33] Association of Official Agricultural Chemists.

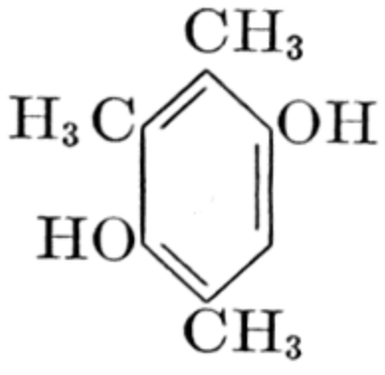
Tocopherol also inhibits gastric secretion of hydrochloric acid and insulin-induced hypermotility of the stomach.

The tocopherols appear to participate as hydrogen carriers in the oxidative cycles of muscle metabolism. Their ability to absorb oxygen can be put to use by employing them as antioxidants. In descending order, δ-, γ-, β-, and α-tocopherol are powerful antioxidants; they are used to stabilize fats and fatty oils against rancidity, and to protect vitamin A and its highly unsaturated provitamins from oxidation. The latter function seems to be also important *in vivo* since in vitamin E deficiency the normal requirement of carotenes may have to be doubled.

Natural sources of the vitamins E are mainly wheat germ oil, cottonseed oil, rice germ oil, lettuce and alfalfa. Concentrates obtained by molecular distillation of vegetable germ oils, stabilized by hydroquinone or ascorbic acid, are used as antioxidants by the food, vitamin and pharmaceutical industries. The source of the vitamins determines their relative prevalence. European wheat germ oil contains largely β-tocopherol, while the American variety is richer in α-tocopherol. This variability is one of the reasons why the medical profession prefers pure racemic synthetic α-tocopherol for clinical purposes.

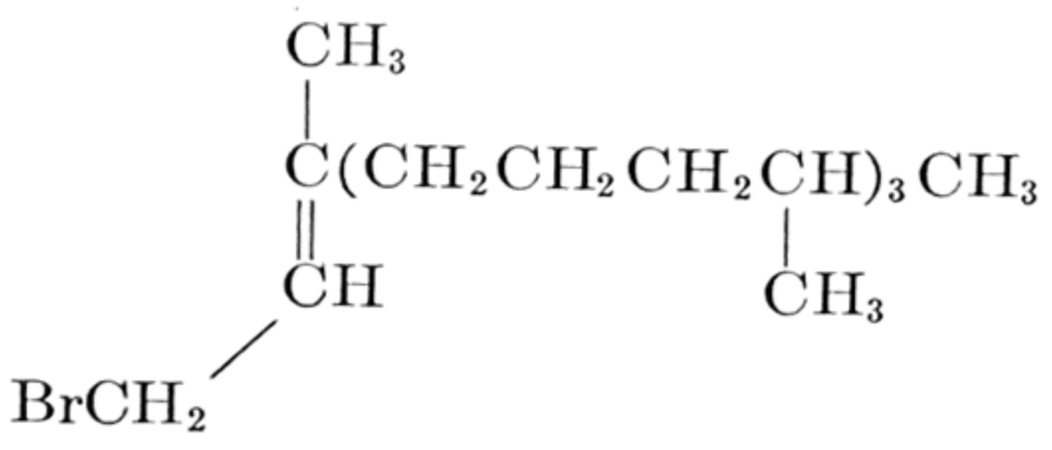
Vitamin E was discovered by H. M. Evans, the structure of α-tocopherol was elucidated by Fernholz,[34] and its synthesis was accomplished by Karrer. Additional work on its chemistry and synthesis has been published in many papers by Lee I. Smith and his coworkers.

The most widely used synthetic method is based on the condensation of the properly substituted alkylhydroquinone (XXVIII-74) with phytyl

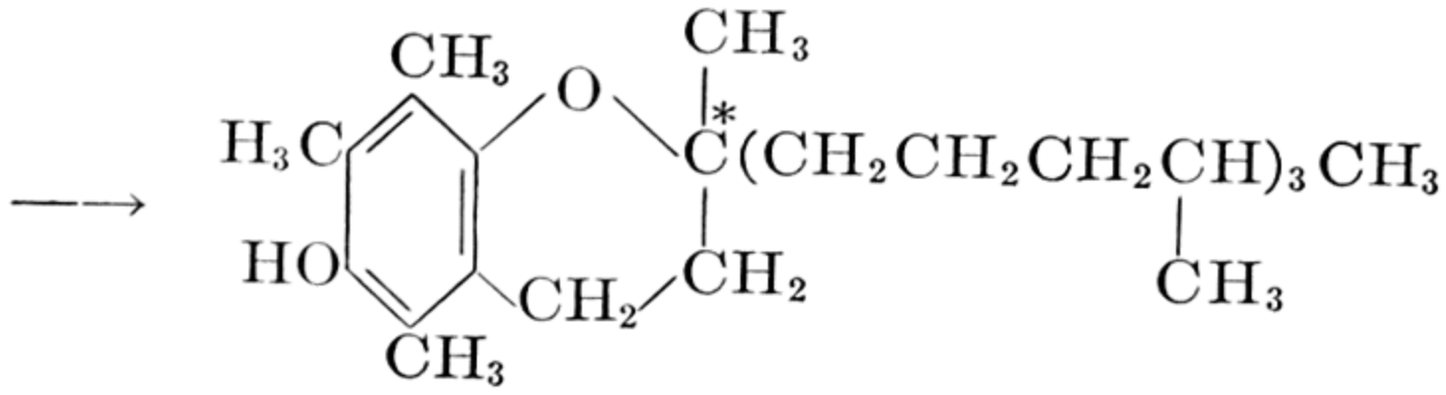


(XXVIII-74)

+



(XXVIII-75)

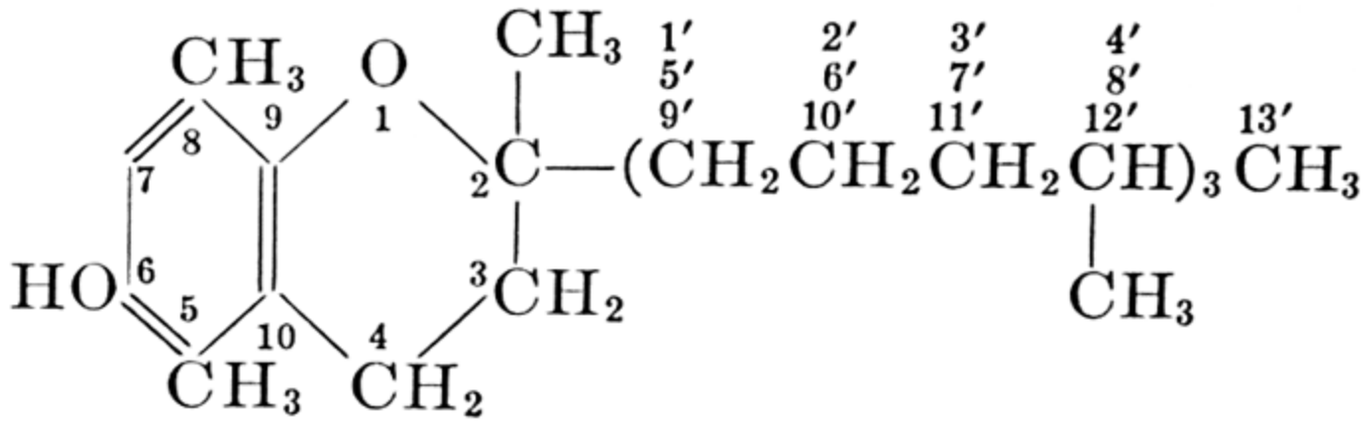


(XXVIII-76)

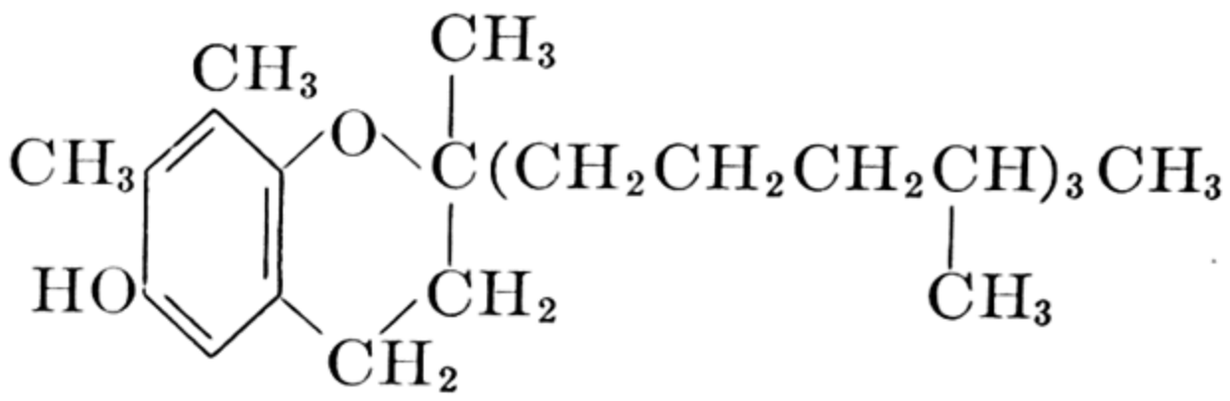
[34] Fernholz, *J. Am. Chem. Soc.*, **59,** 1154 (1934); **60,** 700 (1938). Karrer, Fritzsche, Ringier, and Salomon, *Helv. Chim. Acta*, **21,** 520, 820 (1938).

bromide (XXVIII-75). Phytol or phytadiene can also be used. It is shown here for the preparation of DL-α-tocopherol (XXVIII-76). The natural tocopherols are optically active due to asymmetry in the phytyl chain.

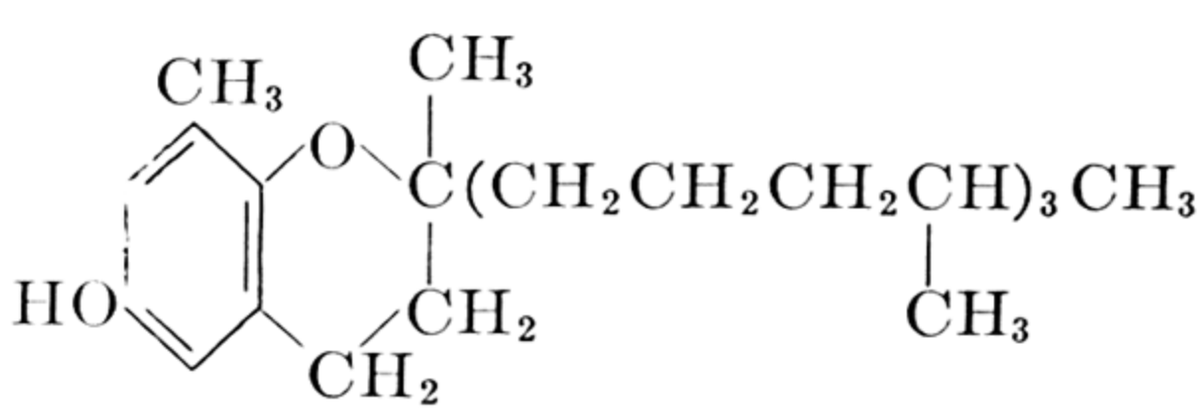
The tocopherols are chroman derivatives and differ from each other by the number and positions of nuclear methyl groups.[35]



(XXVIII-77)



(XXVIII-78)



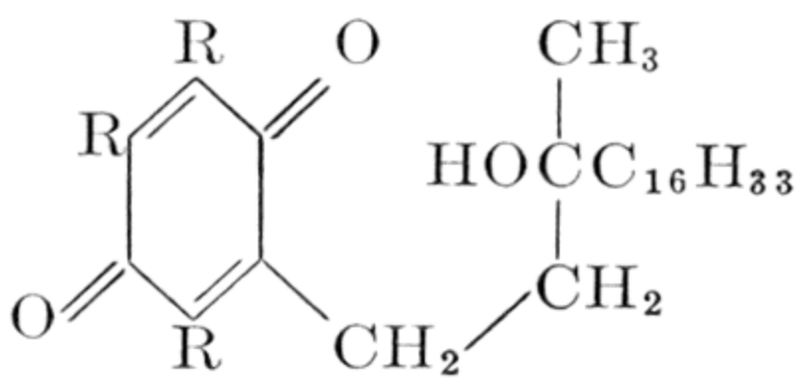
(XXVIII-79)

All four known tocopherols contain a phenolic hydroxyl group *para* to the pyran oxygen. This structural function—the potential oxidizability to a *p*-quinonoid form—is important for the antioxidant power of the compounds but apparently not for their vitamin activity, since α-tocopherol is the most effective vitamin E, the β- (XXVIII-77) and γ- (XXVIII-78) tocopherols are only half as active and the δ-compound (XXVIII-79) has to be given in doses 100 times as high to produce the same effect in rats. Thus the order of vitamin activity of the four compounds is the reverse of their antioxidant power.

[35] The nomenclature of the tocopherols as proposed by Karrer and Fritzsche [*Helv. Chim. Acta*, **21,** 1234 (1938)] regards the vitamins as derivatives of *tocol*, the homolog without nuclear alkyl groups in the benzene ring. The numbering system is indicated in formula XXVIII-77.

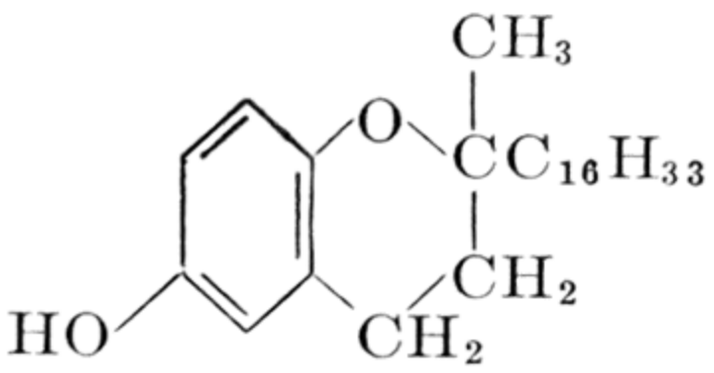
The differences in biological potency between the structurally different tocopherols demonstrate that vitamin E activity might be encountered in other similar compounds as well. Many tocopherol esters are active, and even more active than the free phenols; this holds for the acetate, propionate, butyrate and phosphate of *rac*-α-tocopherol.[36] These esters are probably hydrolyzed slowly to the vitamins in the organism; in accord with this concept, the non-cleavable ethers of the tocopherols are inactive.

The tocopherol quinones (XXVIII-80) which can be obtained by careful oxidation of the vitamins possess no activity. This finding throws some doubt on the suggestion that the vitamins E owe their antioxidant properties to a reversible dehydrogenation to such quinones; if this were true, the latter should be reducible to the phenolic chromans, and should therefore be biologically active.

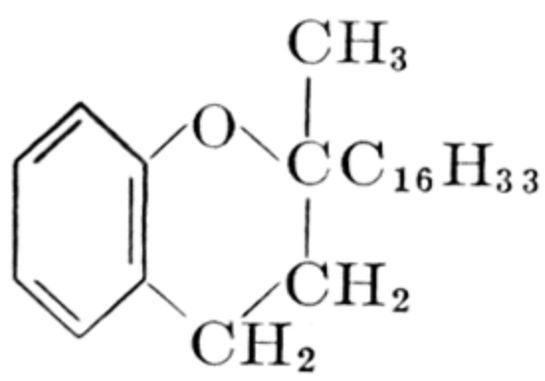


(XXVIII-80)

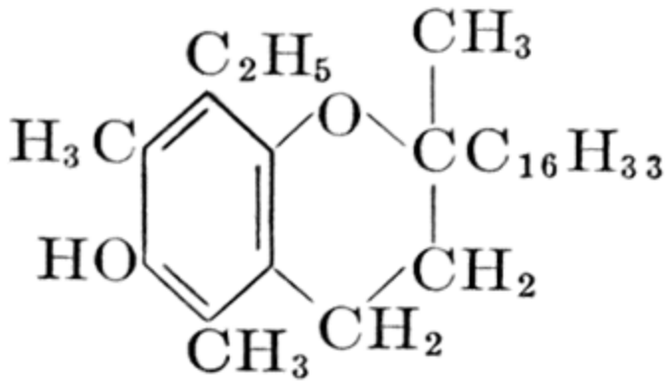
Variations of both the nuclear alkyl groups and the long side chain have shown that vitamin E activity at small dosage levels is fairly specific, but that weak activity at high dosages can be produced by many compounds. The biological tests in these experiments have been performed mostly in rats. Tocol (XXVIII-81) is inactive, and so is 6-desoxytocol



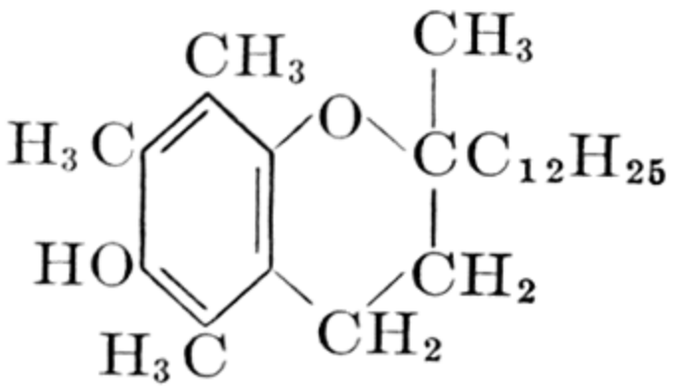
(XXVIII-81)



(XXVIII-82)

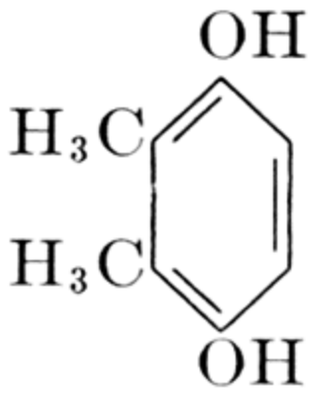


(XXVIII-83)

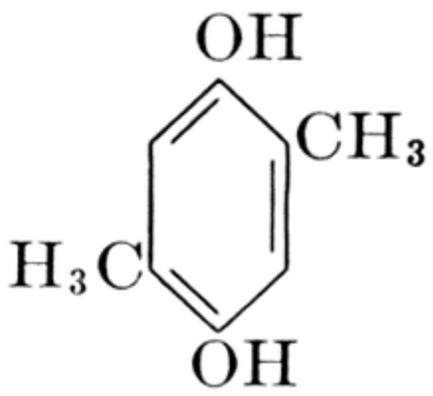


(XXVIII-84)

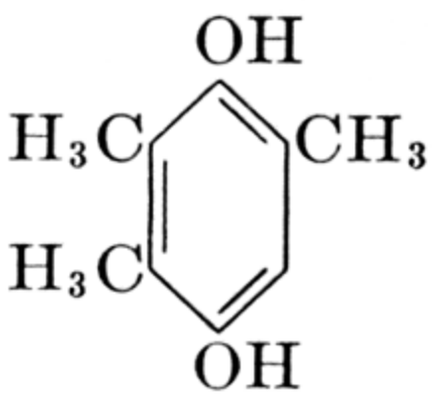
[36] Demole, Isler, Ringier, Salomon, and Karrer, *Helv. Chim. Acta*, **22,** 65 (1939). Karrer and Bussmann, *ibid.*, **23,** 1137 (1940).



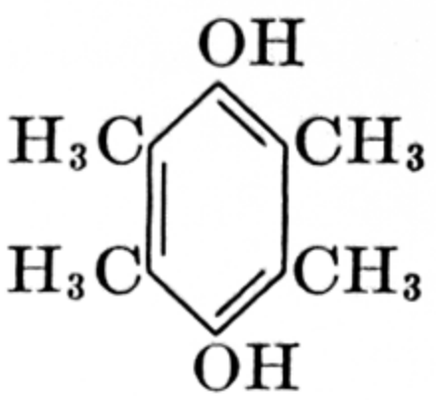
o-Xylohydroquinone



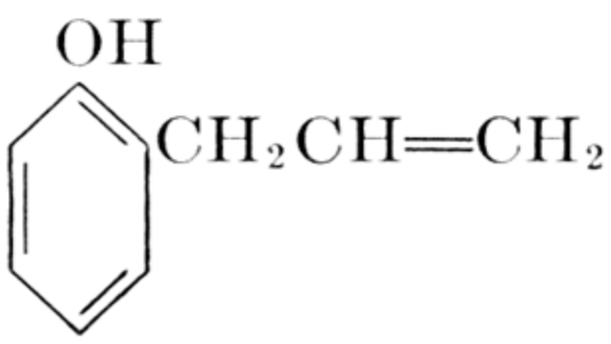
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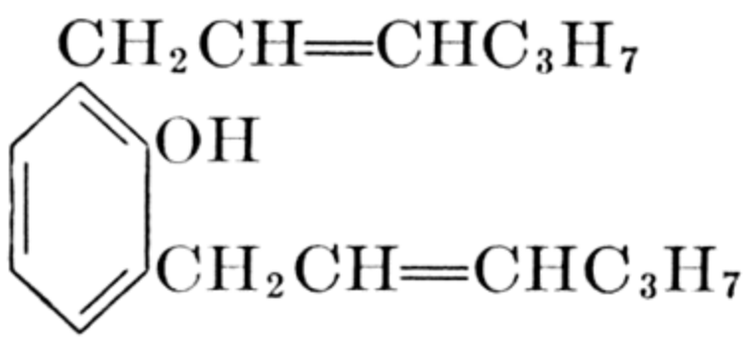
Trimethyl hydroquinone



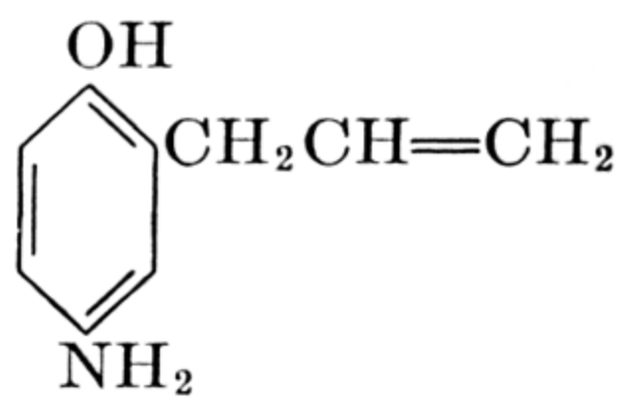
Durohydroquinone



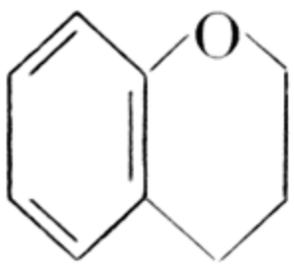
o-Allylphenol



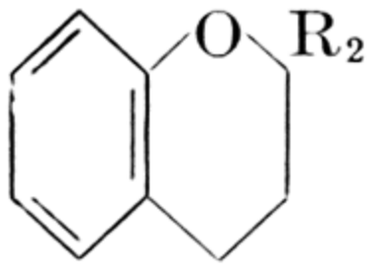
Di-*o*-Hexenylphenol



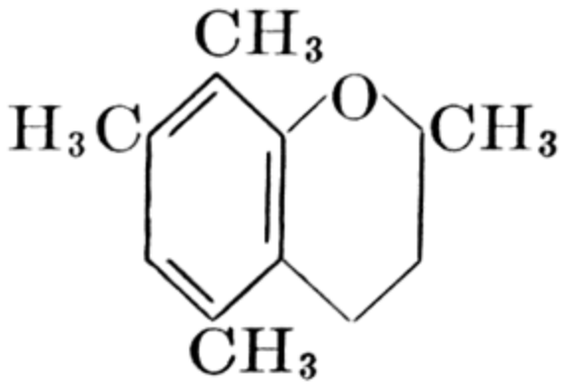
p-Amino-*o*-allylphenol



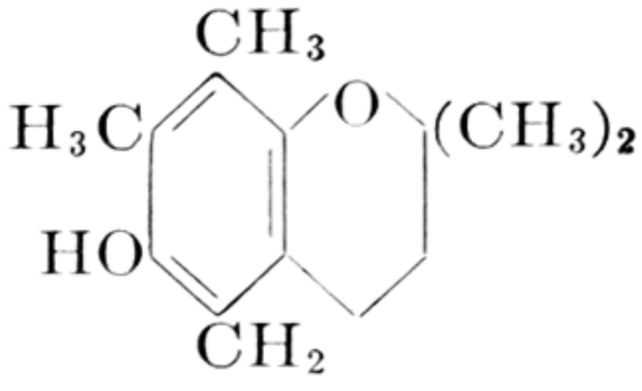
Chroman



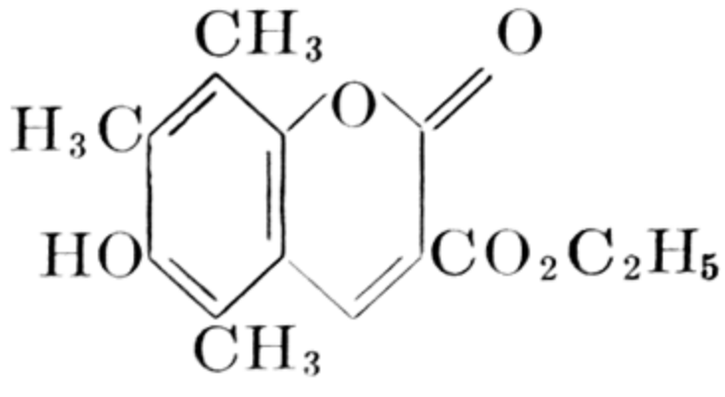
2,2-Dialkylchroman
(R═CH_3; C_4H_9)



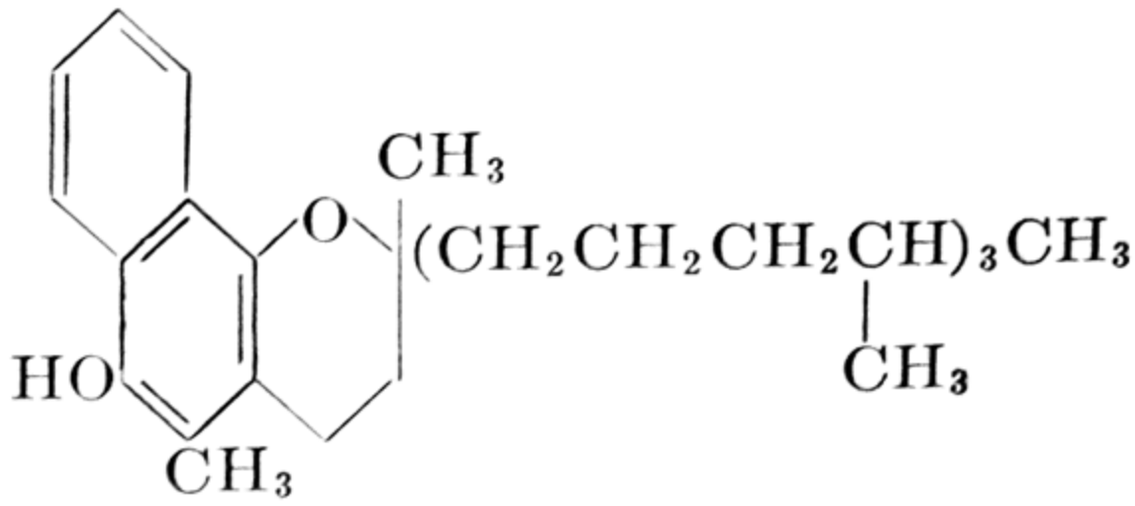
2,5,7,8-Tetramethylchroman



2,2,5,7,8-Pentamethyl-6-hydroxychroman



5,7,8-Trimethyl-6-hydroxy-3-carbethoxycoumarin



Naphthotocopherol

Figure 15. Some Compounds with Weak Vitamin E Activity

(XXVIII-82); the most active alkyl derivatives are 5,7-dimethyl-8-ethyltocol (XXVIII-83) and a diethyl-methyl homolog of undetermined structure.[37]

The structure of the perhydrofarnesyl side chain cannot be altered without serious impairment of vitamin E activity. When the chain is shortened by one or two dihydroisoprene units, that is, by five or ten carbon atoms, respectively, activity is lost; introduction of unsaturation, or replacement of the phytyl group by methyl also result in loss of activity.[38] Weak activity has been found for 2-dodecyl-2,5,7,8-tetramethyl-6-hydroxychroman (XXVIII-84).[39]

When doses thirty to forty times those of α-tocopherol are given, quite a few simple alkylated hydroquinones, their esters and even their ethers, as well as the corresponding quinones exhibit weak activity. Some of these hydroquinones and quinones and some simple coumaran derivatives are pictured in Figure 15. While they provide certain leads for future work, it should be understood that many very similar but inactive derivatives are not listed here for lack of space.[40]

The last compound in Figure 15, naphthotocopherol, is noteworthy in that it exhibits vitamin E activity in medium-large doses while 12 to 24 times this amount produces antihemorrhagic (vitamin K) symptoms. This overlapping of effects is apparently related to the presence of the two structural elements, the 2-methyl-1,4-naphthohydroquinone and the tocopherol portions of the molecule.[41]

7. The Vitamins K

a. The Natural Vitamins

Two naturally occurring derivatives of 1,4-naphthoquinone (vitamin K_1 and vitamin K_2), have been found to be essential nutritional components of enzyme systems which maintain normal coagulation time of blood, and prevent hemorrhages. In contrast to most other vitamins, their place can be taken effectively by a large number of structurally simpler derivatives of 1,4-naphthoquinone or other naphthalene derivatives which can be oxidized readily to the corresponding quinones. One of them, 2-methyl-1,4-

[37] Jacob, Sutcliffe, and Todd, *J. Chem. Soc.*, 327 (1940). Werder, Moll, and Jung, *Z. physiol. Chem.*, **257,** 129 (1939). Karrer and Hoffmann, *Helv. Chim. Acta*, **22,** 654 (1939); **23,** 1126 (1940).

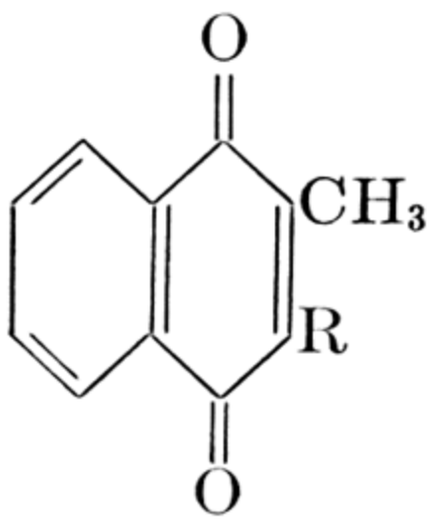
[38] Karrer *et al.*, *Helv. Chim. Acta*, **21,** 939, 1622 (1938); **23,** 581 (1940).

[39] John, Günther, and Schmeil, *Ber.*, **71,** 2637 (1938).

[40] For details, cf. Rosenberg, *Chemistry and Physiology of the Vitamins*. Interscience, New York, 1942, pp. 449–451.

[41] Tishler, Fieser, and Wendler *J. Am. Chem. Soc.*, **62,** 1982 (1940).

naphthoquinone, is a more effective coagulant than the natural vitamins, and possesses a relatively low degree of toxicity. It has been introduced into clinical use under the name of Menadione. The natural K-vitamins contain the same structure (XXVIII-85) but carry in the 3-position a β-unsaturated side chain of four and six isoprene units, respectively.



(XXVIII-85)

(a) Menadione : R = H

(b) Vitamin K_1: R = $CH_2CH{=}C(CH_3)CH_2[(CH_2)_2CH(CH_3)CH_2]_2 \cdot CH_2CH_2CH(CH_3)_2$

(c) Vitamin K_2: R = $CH_2[CH{=}C(CH_3)CH_2CH_2]_5CH{=}C(CH_3)_2$

The vitamins K affect the coagulation of blood by regulating the concentration of prothrombin.This is the zymogen which is converted to the enzyme thrombin in the presence of calcium ions and a normal cell constituent called thrombokinase. Thrombin is the essential catalyst for the conversion of the soluble plasma protein, fibrinogen to the insoluble fibrin which forms the body of blood clots. A more detailed account of these processes and the many proven and hypothetical steps involved has been presented in Chapter XVI, Figure 1.

(a) Precursor of Prothrombin $\xrightarrow[K]{\text{Vitamin}}$ Prothrombin $\xrightarrow[\text{thrombokinase}]{Ca^{++}\text{ and}}$ Thrombin

(b) Fibrinogen $\xrightarrow{\text{Thrombin}}$ Fibrin

In the absence of vitamin K, prothrombin cannot be synthesized, and its concentration drops. Prothrombin synthesis appears to be accomplished in the liver, since normal amounts of vitamin K do not produce adequate prothrombin levels in animals whose liver has been partially extirpated, or in individuals with liver disease. Vitamin K does not coagulate blood *in vitro*, and cannot be detected in prothrombin fractions; it is obviously not present in the zymogen.

The most widely accepted explanation of the role of vitamin K is that it acts as a coenzyme in the processes leading to prothrombin synthesis. It would be attractive to assume that, like other quinones, it acts as a hydrogen carrier in reversible dehydrogenations. Indeed, other 1,4-

naphthoquinone derivatives (phthiocol = 2-methyl-3-hydroxynaphthoquinone, etc.) are evolved by microorganisms to aid in their respiratory processes. Vitamin K_2 is also produced by bacteria including those which inhabit the intestinal tract of many higher animals and man. As mentioned above, derivatives of 1,4-dihydroxynaphthalene have vitamin K activity, and this definitely points to the possibility of their oxidation to the quinones with simultaneous liberation of two utilizable hydrogen atoms. Vitamin K appears to provide the specific optimal conditions for the oxidation of sulfhydryl to disulfide groups;[42] this may also be a critical reaction in the formation of clotted fibrin from soluble fibrinogen.

Vitamin K deficiency and the attending decrease of the prothrombin level of the blood result in a prolonged blood-clotting time, that is, prolonged bleeding, and in hemorrhages. Infants have low prothrombin values at birth, and the hemorrhages frequently observed during their first days of life can best be prevented by administration of vitamins K—or of Menadione—to the mother before birth and during lactation. Avitaminosis-*K* is rare in adults since their intestinal flora provides the requirements of the host. However, in liver or gall bladder diseases, and in ulcerative colitis, the vitamin may not be properly absorbed because of lack of bile or damage to the intestinal wall. Parenteral administration of the vitamins can overcome these obstacles. Vitamins K or Menadione are also given prophylactically to prevent post-operative bleeding, and to avoid abortive hemorrhages during pregnancy.

Vitamin K_1 occurs in leafy vegetables like cabbage, spinach, kale, cauliflower etc., but also in tomatoes, seaweed and in soybean oil. Vitamin K_2 is mainly a product of bacterial metabolism. Of the many complex methods of isolation, the procedure of Fieser has proved most useful.[43] The vitamins are reduced to the hydroquinone stage by means of sodium hydrosulfite, and the dihydroxy compounds are isolated. They can then be reoxidized to the quinonoid vitamins.

The expense of synthesizing vitamin K_1 (see below) has made it necessary to use concentrates of the natural vitamins K, especially those obtained from alfalfa, whenever Menadione cannot be used instead. A limited amount of pure synthetic vitamin K_1 is available; vitamin K_2 has not been synthesized. The use of water-soluble derivatives and analogs of the natural lipophilic vitamins K will be described below.

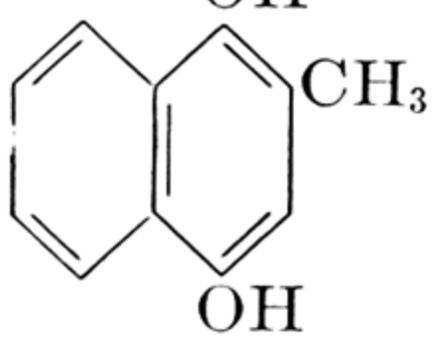
The structure of vitamin K_1 was elucidated by Dam, Karrer, Doisy, Almquist, Fieser and their coworkers both by degradation and by syn-

[42] Bernheim and Bernheim, *J. Biol. Chem.*, **134,** 457 (1940). Baumberger, *Proc. Am. Physiol. Soc.*, 18 (1941).

[43] Fieser, *J. Am. Chem. Soc.*, **61,** 3467 (1939).

thesis.[44] The structural formula of vitamin K_2 was proposed by Doisy.[45]

The synthesis of vitamin K_1 can be achieved by several similar routes. For example 2-methyl-1,4-naphthoquinone, or better its hydroquinone (XXVIII-86), can be condensed with phytol (XXVIII-87) under mildly acidic conditions; if the hydroquinone is used, vitamin K_1–hydroquinone (XXVIII-88) is obtained and this is then oxidized to the vitamin (XXVIII-85b).

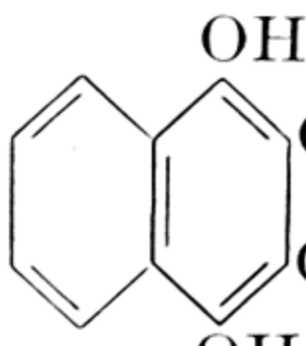


(XXVIII-86)

$$+\ HOCH_2CH{=}C(CH_3)[(CH_2)_3CH(CH_3)]_3CH_3$$

(XXVIII-87)

$\downarrow H^+$



$$CH_2CH{=}C(CH_3)[(CH_2)_3CH(CH_3)]_3CH_3$$

(XXVIII-88)

$\downarrow (O)$

(XXVIII-85b)

This synthesis and similar methods are limited by the difficulty of preparing phytol, phytyl bromide and other compounds necessary for the structure of the long side chain. This problem has not yet been solved economically.[46]

b. Menadione

The other starting material, 2-methyl-1,4-naphthoquinone (XXVIII-89) is readily obtained from 2-methylnaphthalene (XXVIII-90), a by-product of the naphthalene fraction of coal tar. The compound is oxidized to the quinone by the common laboratory oxidizing agents or even by air

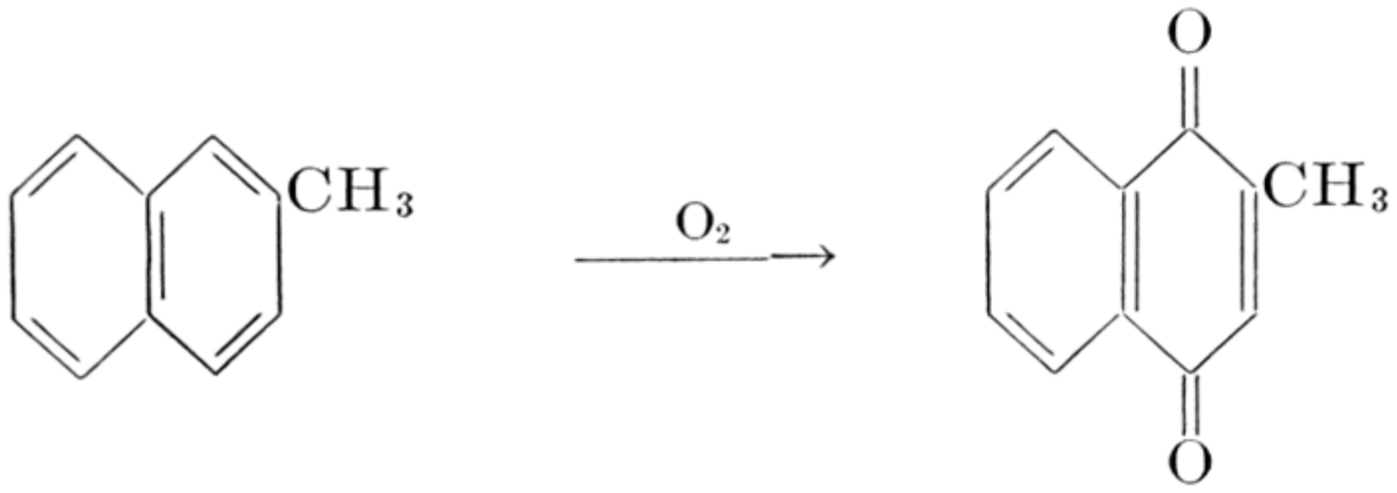
[44] Dam, Geiger, Glavind, Karrer, Karrer, Rothschild, and Salomon, *Helv. Chim. Acta*, **22,** 310 (1939). Doisy *et al.*, *J. Am. Chem. Soc.*, **61,** 1295, 2558 (1939). Almquist and Klose, *ibid.*, **61,** 2557 (1939). Fieser, *ibid.*, **61,** 2559 (1939).

[45] Binkley, McKee, Thayer, and Doisy, *J. Biol. Chem.*, **133,** 721 (1940).

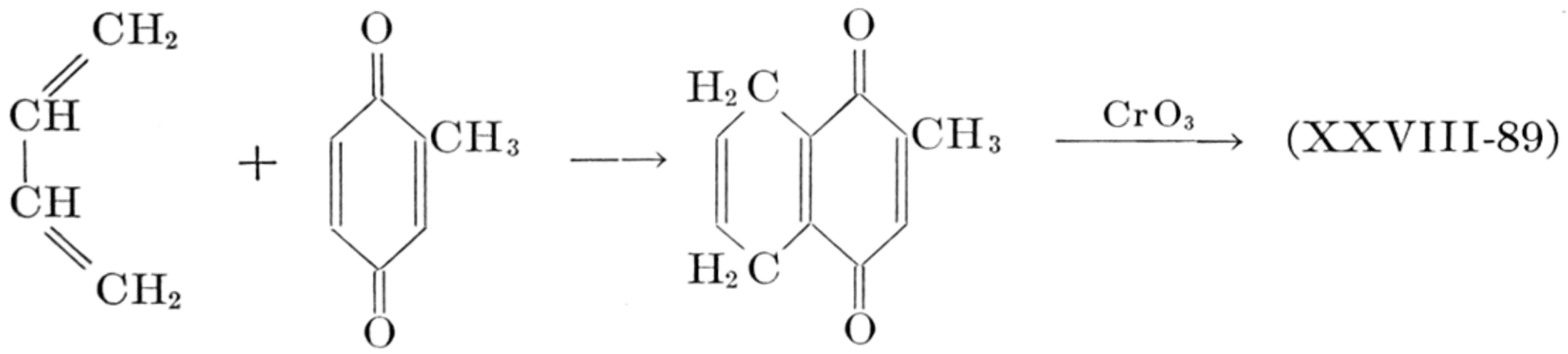
[46] Fischer and Löwenberg, *Ann.*, **475,** 183 (1929).

in good yields.[47] If necessary, 2-methylnaphthalene can also be prepared in good yield from sodium naphthalene-2-sulfonate by the scheme pictured below.[48]

$$2\text{-}C_{10}H_7SO_3Na \xrightarrow{K_4Fe(CN)_6} 2\text{-}C_{10}H_7CN \rightarrow 2\text{-}C_{10}H_7COOH \rightarrow (2\text{-}C_{10}H_7CO_2)_2Ba \xrightarrow{(HCO_2)_2Ba} 2\text{-}C_{10}H_7CHO \xrightarrow{Zn - HCl}$$



(XXVIII-90) (XXVIII-89)



(XXVIII-91) (XXVIII-92)

Another convenient synthesis depends on the addition of butadiene (XXVIII-91) to the dienophil, *p*-toluquinone (XXVIII-92) in acetic acid solution at 110°. The unsaturated intermediate (XXVIII-93) can be aromatized by chromic acid oxidation.[49]

Clinicians welcomed the news of the synthesis of an antihemorrhagic vitamin but a supply of adequate amounts of vitamin K_1 appeared hopeless on the basis of the difficulties besetting the preparation of phytol. Several alkyl analogs, and other intermediates available from the structural proof and synthesis of the vitamin were therefore tested for their effects on speeding up prothrombin clotting time.[50] In the course of these experiments, Ansbacher and Fernholz discovered that 2-methyl-1,4-naphthoquinone (XXVIII-89, Menadione) has two to four times the antihemorrhagic activity of vitamin K_1.[51] To be sure, the natural vitamins K are

[47] Arnold and Larson, *J. Org. Chem.*, **5,** 250 (1940).
[48] Sah, Brüll, and Holzen, *Ber.*, **73,** 762 (1940). Sah, *Rec. trav. chim.*, **59,** 461 (1940).
[49] Ostrozhinskaya, *J. Gen. Chem. (U.S.S.R.)*, **16,** 1053 (1946).
[50] Almquist and Klose, *Biochem..J.*, **33,** 1055 (1939). Quick, *J. Biol. Chem.*, **133,** 78 (1940).
[51] Ansbacher and Fernholz, *J. Am. Chem. Soc.*, **61,** 1924 (1939).

not known to be toxic even in excessive dosages whereas large overdoses of Menadione cause vomiting, porphyrinuria etc. But the therapeutic index of this drug is so favorable (about 1:60) that Menadione has become the most widely used substitute for the natural products. Only few conditions require treatment with vitamin K_1 for optimal results.

It is interesting to speculate about the reason for the high biological activity of Menadione. One could imagine that the natural vitamins K are degraded to the simpler compound *in vivo*, but no experimental evidence for this view has been offered. An attractive hypothesis postulates that Menadione condenses with phytol (from dietary chlorophyll) in the body or in the bacterial cell to yield the natural long-chain vitamins.

c. Other Analogs

It has been possible to draw certain conclusions about the relation of chemical structure and antihemorrhagic activity from the large number of studies on this subject which may be summarized as follows. As long as they can be reconverted readily to the quinones, the corresponding hydroquinones, their esters and even some of their ethers retain largely the activity of the parent compounds. Using vitamin K_1 as a standard, the loss of activity resulting from alterations of its structure is tabulated below.

Table III lists a number of antihemorrhagically active naphthalene derivatives which show at least one-hundredth the activity of vitamin K_1. Their activity is expressed in minimum effective doses which reduce pro-

TABLE II. Effect of Structural Alterations on the Activity of Vitamin K_1

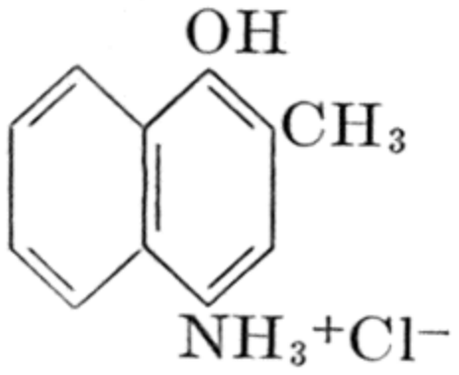
Type of Structural Change	Activity, (Vitamin $K_1 = 1$)
Replacement of 2-CH_3 by higher R	0 to 0.0017
Replacement of 2-CH_3 by H	0.02
Substitution of aromatic ring by CH_3	0
Hydrogenation of aromatic ring	0.008 to 0.025
Hydrogenation of side chain	0.12
Shortening of side chain	0.04 to 0.2
Substitution of phytyl by unbranched side chains	0.11 to 0.33
2,3-Epoxidation	0.8

thrombin clotting time in 60 to 80% of vitamin K-deficient chicks to less than ten minutes over an 18-hour test period.[52]

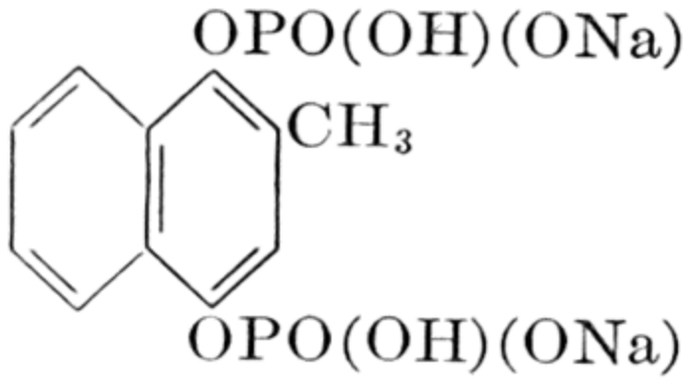
Because both the natural vitamins K and Menadione are insoluble in water and must be administered parenterally in oil solutions, water-soluble derivatives have been sought. Such substances have been found among compounds which can be converted to the corresponding quinones by oxidation, reduction, or by two step reactions involving hydrolysis and

[52] Fieser, Tishler, and Sampson, *J. Biol. Chem.*, **137,** 659 (1941).

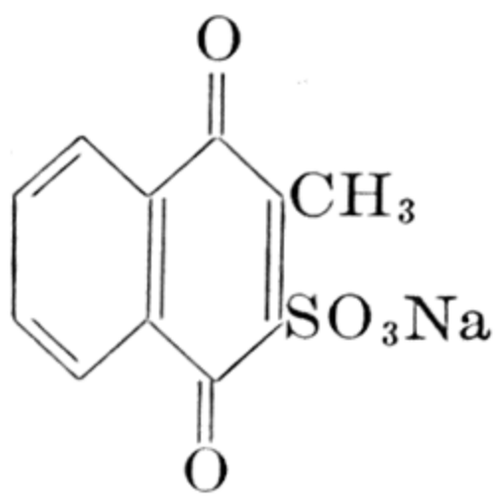
oxidation. The most widely used drugs in this group are 2-methyl-4-amino-1-naphthol hydrochloride (XXVIII-94), sodium 2-methyl-1,4-dihydroxynaphthalene diphosphate (XXVIII-95), and sodium 2-methyl-1,4-naphthoquinone-3-sulfonate (XXVIII-96). The useful activity of the latter is surprising since the introduction of a sulfonic acid group into the molecule of a physiologically active drug so often abolishes all biological effects.



(XXVIII-94)



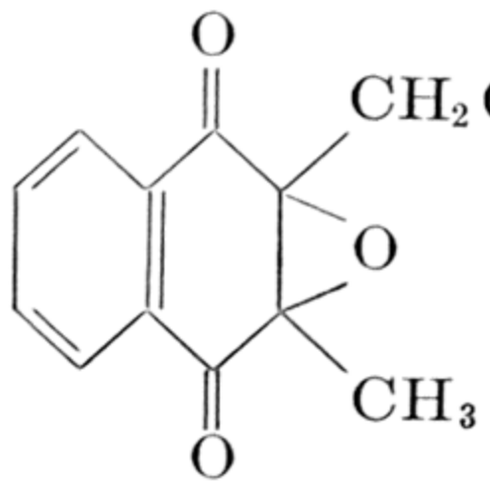
(XXVIII-95)



(XXVIII-96)

In addition to naphthalene derivatives certain phenols and simple quinones in other nuclear series can also exert antihemorrhagic activity. *p*-Xyloquinone and 8-hydroxyquinoline are examples of such compounds.

The 2,3-epoxides of vitamin K_1 (XXVIII-97) and of Menadione are also used as antihemorrhagic drugs. They can be prepared from the parent quinones by oxidation with hydrogen peroxide in an alkaline dioxane medium.

(XXVIII-85b) $\xrightarrow{H_2O_2}$ 

(XXVIII-97)

These epoxides are colorless oils and form stable 10% emulsions with aqueous-alcoholic solutions of glucose which are suitable for intravenous injections.

The antihemorrhagic activities of some of these water-soluble derivatives can be compared by consulting Tables III and IV on page 566 following.

TABLE III. ANTIHEMORRHAGIC ACTIVITY OF SOME NAPHTHALENE DERIVATIVES

Compound	Minimum effective dose, γ
Vitamin K_1	1
Vitamin K_2	1.6
2-Methyl-3-farnesyl-1,4-naphthoquinone	5
β,γ-Dihydrovitamin K_1	8
5,8-Dihydrovitamin K_1	4
2-Methyl-3-geranyl-1,4-naphthoquinone	25
2-Methyl-3-cinnamyl-1,4-naphthoquinone	25
2-Methyl-3(β,γ,γ-trimethyl-allyl)-1,4-naphthoquinone	50
2,3-Dimethyl-1,4-naphthoquinone	50
2-Methyl-1,4-naphthoquinone (Menadione)	0.3
2-Methyl-1,4-dihydroxynaphthalene	0.5
2-Phytyl-1,4-naphthoquinone	50
2-Methyl-3-carbethoxy-1,4-dihydroxynaphthalene	25
2-Hydroxy-1,4-naphthoquinone (Lawsone)	10
2-Hydroxy-3-dimethylallyl-1,4-naphthoquinone (Lapachol)	5
2-Methyl-2-phytyl-2,3-dihydro-1,4-naphthoquinone	50
2-Methyl-4-amino-1-naphthol hydrochloride	about 1
3-Methyl-4-amino-1-naphthol hydrochloride	about 1
2-Methyl-1-Naphthylamine	5
2-Methyl-5,8-dihydro-1,4-dihydroxynaphthalene	6
2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone	8
2-Methyl-1-naphthol	1
3-Methyl-1-naphthol	0.6
2-Methyl-1-tetralone	0.6
3-Methyl-1-tetralone	1

TABLE IV.[52] ANTIHEMORRHAGIC ACTIVITY OF NAPHTHOQUINONE EPOXIDES, AND ESTERS AND ETHERS OF 1,4-DIHYDROXYNAPHTHALENE DERIVATIVES

Compound	Minimum effective dose, γ
Vitamin K_1-2,3-oxide	1.2
2-Methyl-1,4-naphthoquinone-2,3-oxide	5
2,3-Dimethyl-1,4-naphthoquinone-2,3-oxide	25
Vitamin K_1 hydroquinone diacetate	2
Vitamin K_1 hydroquinone diphosphoric acid	50
Na 2-methyl-1,4-naphthohydroquinone diphosphate	0.5
Na 2-methyl-1,4-naphthohydroquinone disulfate	2
2-Methyl-1,4-diacetoxynaphthalene	1
2-Methyl-1,4-dibenzoxynaphthalene	1
1-Hydroxy-2-methyl-4-methoxynaphthalene	1
2-Methyl-1,4-dimethoxynaphthalene	5
2-Methyl-1,4-dibenzyloxynaphthalene	7
Vitamin K_2 hydroquinone diacetate	3.2

d. Non-quinoid Blood Coagulants

The coagulation of blood can be accelerated by compounds other than those discussed on the preceding pages. Several other vitamins and hormones carry out the same function although not as effectively as the compounds in the vitamin K group. Both ascorbic acid and vitamin D have been used in post-operative stilling of bleeding. Epinephrine and the parathyroid hormones decrease coagulation time, perhaps by increasing the calcium ion level in blood, in any case by raising the amount of thrombin and thrombokinase. Nor is coagulant activity restricted to biocatalysts in the narrower sense of the word. The thionine dyestuff, Toluidine Blue, shortens blood clotting time after radiation sickness, and the totally unrelated nitrogen mustards (Chapter XXVII) have a similar effect.

SUBJECT INDEX

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